Archives of Internal Medicine

VOLUME 51 MAY, 1933 NUMBER 5

HYDROPHOBIA

REPORT OF TWO FATAL CASES WITH PATHOLOGIC STUDIES IN ONE

DAVID RIESMAN, M.D.

W. W. FOX, M.D.

B. J. ALPERS, M.D.

AND

DAVID A. COOPER, M.D.

PHILADELPHIA

In recent years rabies in man has become a rare disease, owing to the improved methods of prophylactic treatment and to laws requiring the registration of all dogs and the quarantining of any suspicious animals. We have observed two cases, one of which developed in spite of the accepted prophylactic treatment. The other was that of a woman, aged 22, who was admitted to the Philadelphia General Hospital on April 5, 1931. The report of this case must of necessity be incomplete, because the patient was in the hospital only eighteen hours and was so desperately ill and so agitated that all efforts had to be centered on treatment. Furthermore, the family refused to permit an autopsy, and the coroner on whom the responsibility ultimately fell did not investigate the case. The history that we obtained is a digest of information received from the patient herself on admission, from her brother, her mother and the hospital in which she was first treated. Where there was disagreement, an attempt has been made to follow what in our judgment seemed the most reliable authority.

REPORT OF CASES

CASE 1.—Mrs. C. P., a housewife, aged 22, was admitted to the Philadelphia General Hospital on April 5, 1931. The family history was negative, as was her past medical history. She was married at the age of 18, and had two children. She believed herself about two months pregnant. Her husband was living and well, but their married life had been stormy. He drank heavily, and on occasions her brothers had to protect her from his violence.

About two months before admission, on February 5, the patient was bitten by a dog. This dog, which had just been given to her husband as a pet, also bit him, and at least two or three other persons in the neighborhood. Because of this her husband returned it to the original owner, and it was subsequently killed in a dog fight. Mrs. P. was taken to a nearby hospital, where the wounds were described

Read at the meeting of the College of Physicians, Section on Medicine, Philadelphia, April 27, 1931.

as "four small puncture wounds on the left wrist." They were treated with nitric acid, ammonia, iodine, alcohol and a dry dressing.

On Friday, April 3, she complained of pain in her left arm and in her back. On the following day she felt worse. Her husband went out for medicine and did not return. She went to her mother's home; she was much agitated, and said that she was leaving her husband. She complained of tightness in her chest, and declared that she could not swallow anything. She was taken to a hospital where

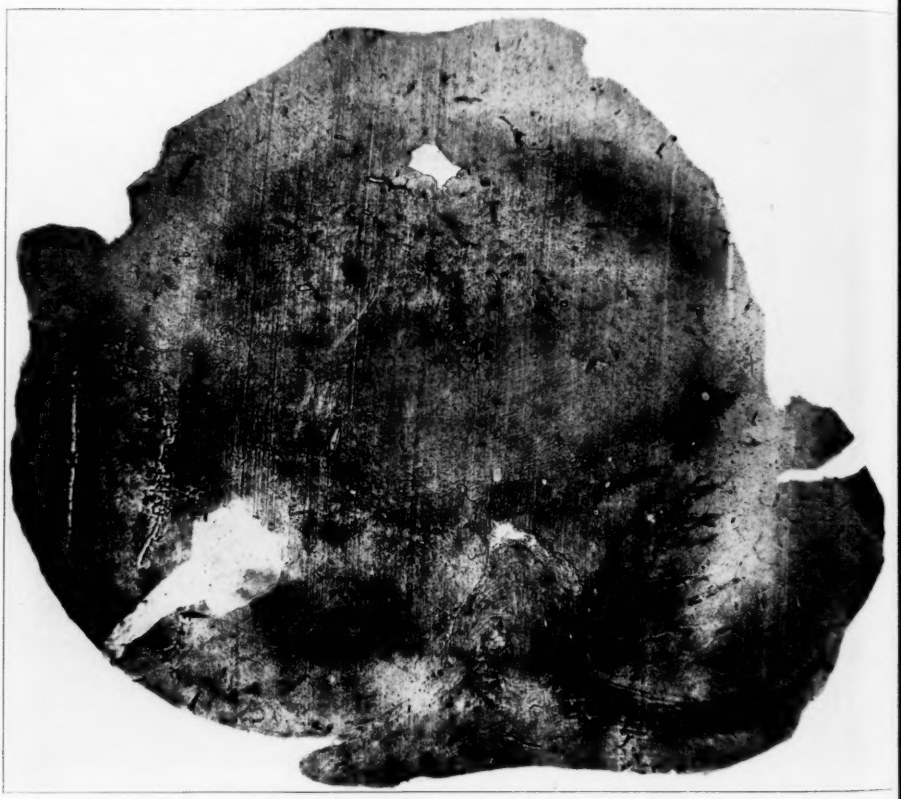


Fig. 1.—A section through the midbrain showing the vessels infiltrated, especially in the colliculi, periaqueductal region and reticular substance; toluidin blue stain.

she was told that she was all right. After she returned home, a doctor was called, who tried to give her some medicine. She choked on it, insisted that she could not swallow, and began to have "fits," characterized by screaming, gripping her chest and crying out that she could not breathe, and that air from an open door or window choked her. Her brother then took her to two other hospitals, at each of which a hypodermic injection of some sort was administered. Finally, two days

after the onset of symptoms, she was sent to the Philadelphia General Hospital. When first seen she was sitting up in bed and looking around apprehensively. She complained of a tight feeling in her chest, inability to swallow and difficulty in breathing. An open door or window made a draught that choked her. She

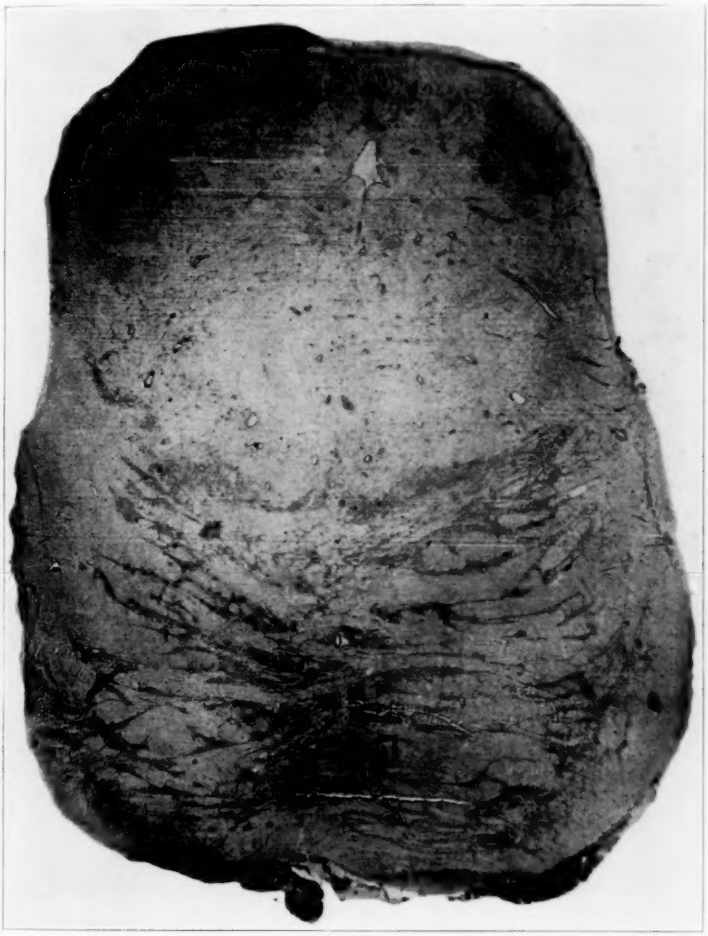


Fig. 2.—A section through the pons showing the infiltration, chiefly in the tegmentum and the reticular substance, with the basis pontis untouched; toluidin blue stain.

objected to examination, insisting that each touch "choked" her. A fairly complete physical examination was achieved, however, during the course of the day. The findings were negative, except for widely dilated pupils which failed to react

to light or in accommodation, and a scanty, thin, white vaginal discharge. Her color was good, and despite her claims of difficult respiration, breathing was not noisy, and there was no cyanosis. The axillary temperature was 101.8 F., and the pulse rate, 120. During the morning she refused all medicines and complained that a proctoclysis choked her; she occasionally grasped the top of the bed and screamed loudly. The nurse was eventually able to soothe her, and even persuaded her to leave the door of her room ajar. She apparently drank water placed beside her when no one was looking. At noon she drank a cup of orange juice and ate

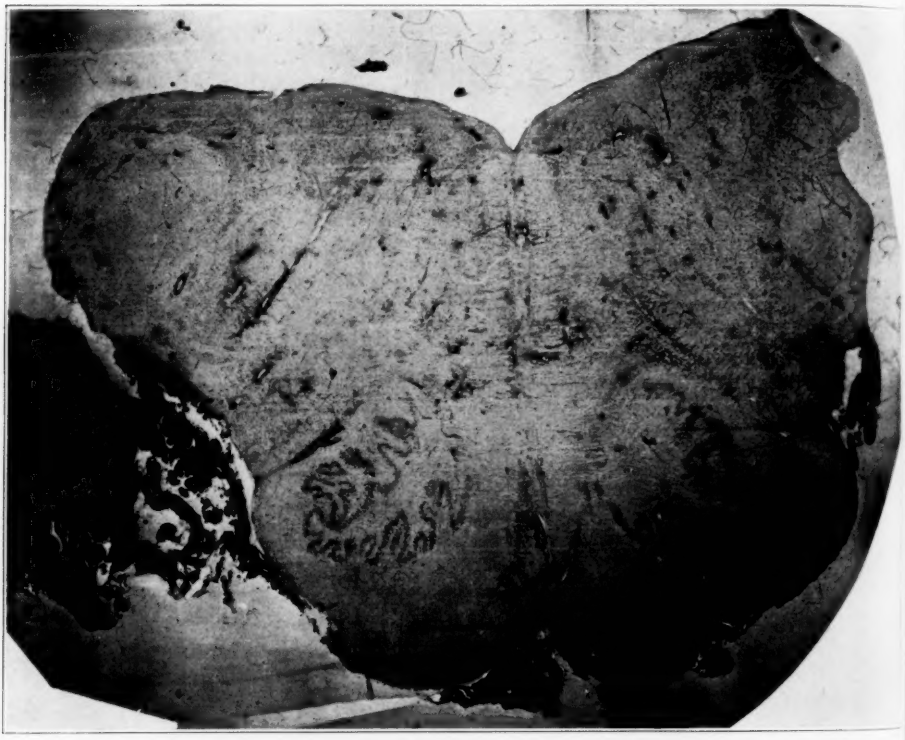


Fig. 3.—A section through the medulla showing the exudate, chiefly in the floor of the fourth ventricle and the reticular substance. Most of the exudate lies above the inferior olives; toluidin blue strain.

small helpings of chicken, potatoes and rice pudding, but refused water. There was no excessive salivation.

In the afternoon she became more and more excited. She was worried if the door of her room was allowed to be open. When it was closed, she complained that there was a nurse just outside the door. She insisted that the windows were open when they were not. Eventually, she began to curse and spit at every one, to scream loudly and to void involuntarily. The pulse became rapid; the color

became slightly bluish. She was put in restraint and ¼ grain (0.016 Gm.) of morphine sulphate and 1/150 grain (0.0003 Gm.) of hyoscine hydrobromide were given, after which she was transferred to the psychopathic department. In the evening she began to vomit a brown liquid. She also spat frothy white saliva, and the nurses reported that she was frothing at the mouth. She no longer screamed but lay talking and muttering to herself. At 10 p. m. the pulse became imperceptible; the color, pale and bluish; the axillary temperature was 103 F. At 11 p. m. the temperature was 106.4, and at 11:30 she died.

The diagnosis must obviously remain uncertain, although the case is entered on the hospital records as one of hydrophobia. So far, none of the other persons bitten by the dog has had any unfavorable symptoms. Since the patient's death, however, antirabic treatment has been instituted on all except her husband, who refused it.

Case 2.—The second case was that of a boy, aged 14 years, who was admitted to the University Hospital on Nov. 5, 1930, with fever, nervousness and instability

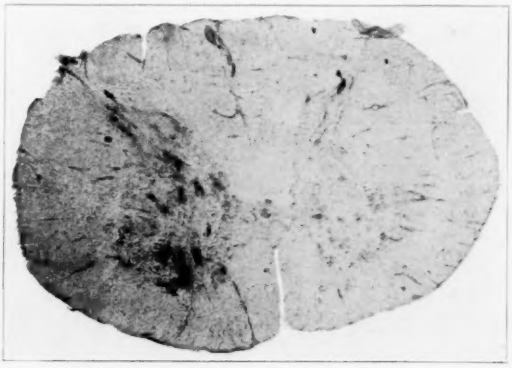


Fig. 4.—A section through the cervical cord showing the inflammation almost entirely in the gray matter; toluidin blue stain.

and salivation. He had been bitten by a stray dog on Oct. 11, 1930, twenty-five days prior to admission. The animal had a bloody mouth, as though it had been injured, and the boy was trying to aid it when he was bitten. The dog had disappeared and could not be located. The bite, which involved the left ear and cheek, was treated immediately in the Atlantic City Hospital, the wound being cauterized with phenol. Two days after the injury, the Pasteur prophylactic treatment was instituted, and a full course of treatment was given, which was completed a few days prior to admission. There were no untoward reactions. The local wounds had healed completely during that time. Throughout the week prior to admission the child had been more irritable than usual, and three days before he had complained of headache and had a coated tongue. He received a laxative, which he vomited. The next day he had a temperature of 101 F., and the headache was worse. He also complained of numbness and tingling in his left cheek and ear. These symptoms increased rapidly, and in addition, internal strabismus, diplopia and visual hallucinations appeared. The boy was restless and sleepless, and had difficulty in swallowing.

The past medical, family and social history was irrelevant.

When the boy was seen by one of us (D. R.), the most striking features were an intense restlessness, a flushed face and a continued flow of water from the mouth. The mouth seemed to be filled with saliva. Though the patient was conscious and could answer questions he seemed to have visual hallucinations with respect to surrounding objects. The temperature was 101 F., the pulse rate, 120. The lungs showed many coarse râles. The skin over the trunk and extremities was markedly hyperesthetic, but there were no paralyses of the limbs and no spasticity. The knee jerk was exaggerated. The right eye showed an internal strabismus; the pupils were dilated. Examination of the blood revealed hemoglobin, 90 per cent; red blood cells, 4,750,000; white blood cells, 26,200, of which 80 per cent were neutrophils, 10 per cent lymphocytes and 10 per cent monocytes.

Despite sedative treatment, the boy had several generalized convulsions. The temperature rose steadily to 107 F., and death occurred in a convulsion, six hours after admission.

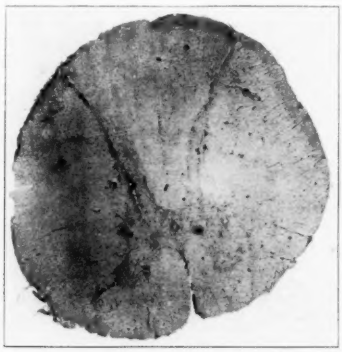


Fig. 5.—The thoracic cord shows much less infiltration than the cervical cord.

The diagnosis was hydrophobia—acute encephalitis. The autopsy was performed shortly after death. The findings, except those in the brain and spinal cord, were insignificant.

Gross Morbid Anatomy.—The brain and spinal cord showed little in the gross specimen. The brain was markedly edematous everywhere. It had a blue cyanotic appearance, owing to congestion of all the superficial vessels. The substantia nigra appeared somewhat depigmented. The spinal cord showed nothing of importance grossly, except a pinkish appearance of the gray matter, owing to the great prominence of the vessels. It, too, was swollen and edematous.

Microscopic Changes.—In the gray substance of the base of the brain and in the gray matter of the spinal cord there was a marked inflammatory exudate, which was confined largely to the vessels, but which was spread diffusely throughout these tissues. The ganglion cells of the cortex showed marked changes.

The distribution of the lesions is a matter of great interest. The most pronounced reaction was found at the base of the brain. The cortex showed almost no evidence of inflammation, except for a mild meningeal exudate in a few places. Of the basal ganglia, the thalamus showed some active perivascular inflammatory foci. These were situated just under the ventricular ependyma. The other basal ganglia were relatively little involved. In the mesencephalon the inflammatory

reaction was most marked in the colliculi, around the aqueduct of Sylvius and in the reticular substance. The nucleus ruber was mildly infiltrated, and so, too, was the substantia nigra. The pes pedunculi showed some inflammatory foci. The greatest infiltration in the mesencephalon was in the periaqueductal gray matter, immediately around and below the iter. Infiltration tended to shade off gradually below this, though it was present everywhere in this section of the brain stem. The inflammatory reaction in the pons was practically confined to the tegmentum. The gray matter around the iter and fourth ventricle was markedly infiltrated with the reacting cells, but the basis pontis remained untouched. This was exceedingly striking. The entire tegmental gray matter was infiltrated and involved in

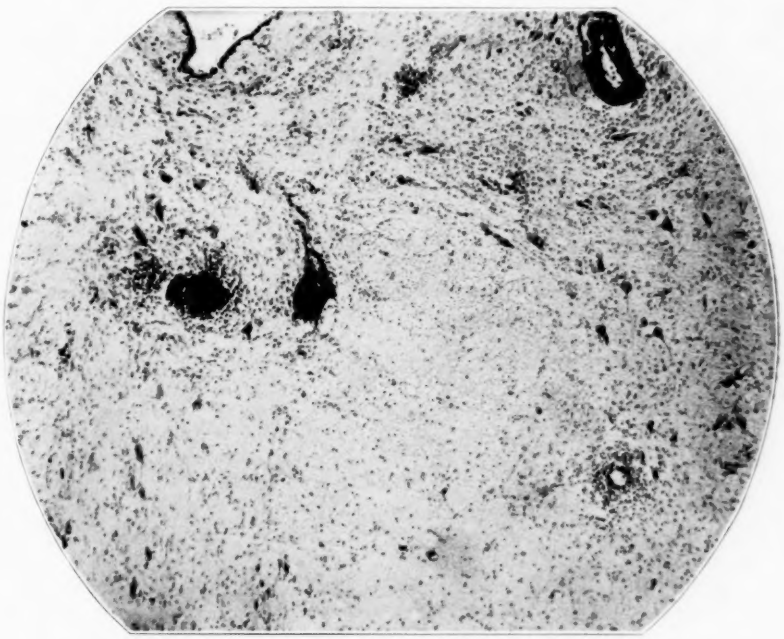


Fig. 6.—Perivascular and vascular infiltration just under the aqueduct of Sylvius; toluidin blue stain.

the pathologic process. In the medulla the inflammation was found in the floor of the fourth ventricle and in the entire reticular substance. Here, too, the inflammation was confined practically entirely to the gray matter. It stopped at the level of the inferior olives. The latter were mildly infiltrated. As one descended from the medulla into the spinal cord, it was found that the gray matter was involved almost exclusively. The white substance was infiltrated mildly here and there, but practically all the changes were in the gray substance. The cervical and lumbar cords were severely involved, while the thoracic region was less severely attacked. Within the gray substance the anterior horns were more markedly affected than the posterior horns. It is thus evident that the process was confined almost entirely to the gray matter of the base of the brain and the spinal cord.

The nature of the exudate is of as much interest as its distribution. In the areas where the exudate was most pronounced, there was marked perivascular infiltration. This involved the adventitial sheaths of the blood vessels as well as the perivascular spaces. In some vessels the amount of exudate was tremendous; in others it was less pronounced. In some vessels the exudate was composed exclusively of lymphocytes; in others it consisted of lymphocytes and large mononuclear elements. Plasma cells were rarely seen. Around the vessels, within the tissue substance, were large groups of cells of noninflammatory nature. They were composed of large oval, round or crescentic vacuolated nuclei and an abundant

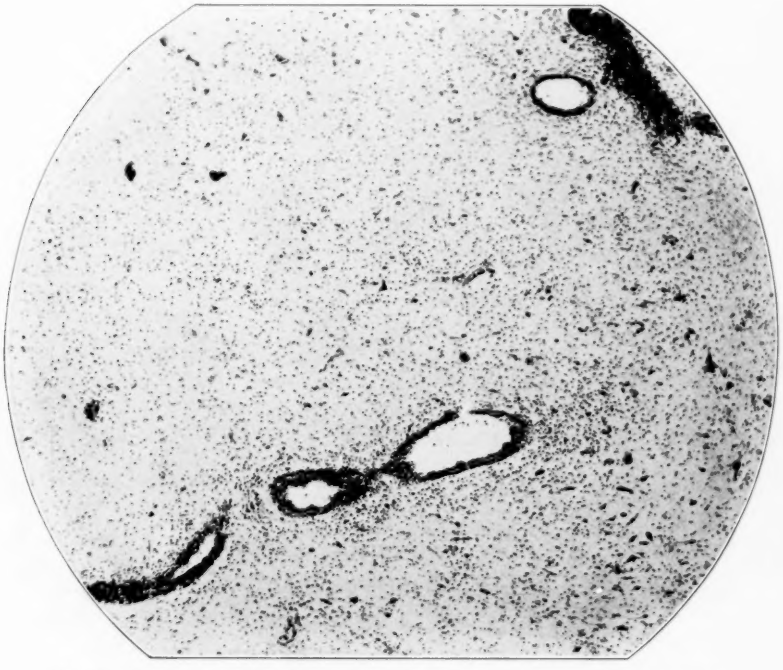


Fig. 7.—Inflammation in the floor of the fourth ventricle; toluidin blue stain.

cytoplasm. They probably represented astrocytes among which were some fibroblastic elements. In some areas these cells constituted the major portion of the cellular reaction. They were spread throughout the involved areas, sometimes around vessels, but most often as a diffuse reaction within the tissue substance itself. They were particularly abundant in the spinal cord.

The meninges over the cortex, base of the brain and cord were mildly infiltrated here and there with lymphocytes. This meningeal infiltrate was, however, nowhere pronounced.

The cells of the cortex were almost universally degenerated. So, too, were the ganglion cells in the inflammatory areas and in the spinal cord. In the latter, the ganglion cells were virtually gone, but at a few levels groups of relatively intact

ganglion cells could be found. The cells in the cortex were swollen, their processes tortuous and enlarged, the nucleus homogeneous, the nuclear membrane absent, giving a poor differentiation between nucleus and cytoplasm, the nucleolus vacuolated and the cytoplasm without Nissl bodies. This sort of ganglion cell change was found in all the cortical layers and in all areas of the brain. There was no glial hyperplasia in the cortex.

The oligodendroglia was acutely swollen in the spinal cord. The astrocytes showed no changes in either the brain or the cord. Neurofibrillar stains showed an absence of neurofibrils within the anterior horn cells of the spinal cord.

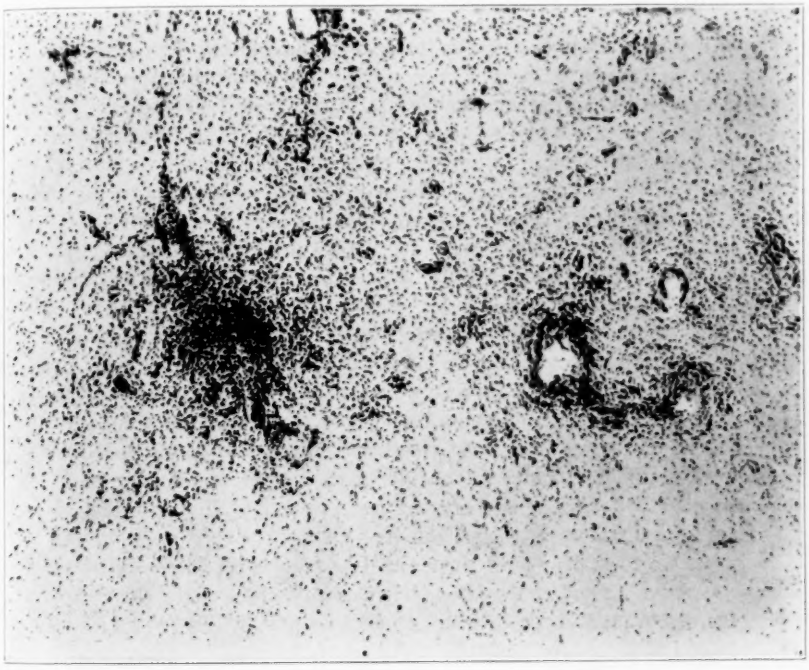


Fig. 8.—Marked infiltration with lymphocytes and neuroglia in the anterior horn of the cervical cord. Note the paucity of ganglion cells; toluidin blue stain.

An extremely careful search for Negri bodies failed to reveal these inclusions in the ganglion cells of the brain or spinal cord. However, four rabbits into which intracranial injections of an emulsion of the brain tissue had been made died on the tenth, eleventh, eleventh and fifteenth days respectively, the symptoms being those of rabies; at autopsy, typical Negri bodies were found, thus confirming the diagnosis of rabies.

PATHOLOGY OF RABIES

The pathologic changes in the nervous system in rabies are characterized by the presence of both inflammatory and degenerative

products. Schaffer first called attention to these two processes in cases of lyssa. The inflammatory changes are characterized by a lymphocytic infiltration of the vascular adventitia in the early stages of the disease, followed by a filling of the perivascular lymph spaces with inflammatory cells, and eventual infiltration of the parenchyma. Lymphocytes constitute the majority of the exudative cells; plasma cells are less abundant; polymorphonuclear cells are rarely seen. The inflammation is accompanied by proliferative changes on the part of the neuroglia of both a diffuse and a focal nature. Babes described glial foci which he considered characteristic of rabies, but his descriptions have not been widely accepted. Achucarro has observed proliferative changes in the neuroglia, especially in the cornu ammonis. In addition, he found typical rod cells containing fat droplets in the cornu. Collado described hypertrophy of microglia cells in rabies. This has also been found by Loewenberg. In our own case, the glial reaction was intense throughout the entire involved area, varying in intensity apparently in direct proportion to the severity of the inflammation. Most of the neuroglial cells are astrocytes. In our case the oligodendroglia, especially in the spinal cord, reacted by an acute swelling. The microglia took no part in the process.

The degenerative changes found in the nerve cells of the cortex and elsewhere are not as a rule in proportion to the degree of the inflammatory changes. There may be pronounced evidences of inflammation and only mild degenerative changes in the nerve cells of the brain. The reverse is also found—the degeneration of the cells may be pronounced and universal and inflammatory evidences only slight. Klarfeld believes that there are two separate and distinct processes in rabies: inflammatory and degenerative. These have apparently no clear relationship to each other. In one of his patients he found inflammatory changes limited to the pons and medulla and degenerative changes in the cerebrum and cerebellum. In another patient there were Babes' nodules and inflammation in the spinal cord, with no inflammation but active degeneration in the cerebrum and cerebellum. Spatz believes that the independent degenerative changes in the nerve cells may play an active rôle in the disease. The degeneration in the ganglion cells of the cortex is manifested by poor staining of the cell body, a loss of Nissl bodies, the formation of small bodies of chromatin in the nucleus, vacuolization, fatty degeneration, sclerosis and pigment atrophy. In our case the ganglion cells were swollen, the processes unduly visible, swollen and tortuous, the cytoplasm without Nissl bodies or with pulverized remains of these, the nucleus homogeneous and pale, the nucleolus often vacuolated and the cells containing fat. Cajal has described a simplification of the fibrillar network in the ganglion cells in rabies

with some th ckening of the neurofibrils, especially at the edge of the cells. This has been confirmed by Achucarro, who found these changes in the spinal ganglion cells. The change occurs late in the disease.

The independence of the inflammatory and degenerative processes is well illustrated in our case, in which there was marked inflammation at the base of the brain and in the spinal cord, and universal ganglion cell degeneration in the cortex, with practically no evidence of inflammation in this part of the brain. The independence of the two processes must not be overemphasized, however, because there were pronounced degenerative changes in the ganglion cells within the infiltrated areas of the brain. In the cortex, however, degeneration was pronounced, without the inflammation which was so marked at the base of the brain. There may, therefore, be two processes going on at the same time: inflammatory at the base of the brain and degenerative in the cortex. The degree of intensity of the degenerative process is not dependent in any way, apparently, on the inflammatory change. This point is well illustrated in two cases reported by Schükri and Spatz. In one case, there were inflammatory changes of a pronounced degree at the base of the brain, with only mild degenerative changes in the ganglion cells within the inflamed areas and practically no degeneration of the ganglion cells in the cortex. In their second case, there were likewise pronounced inflammatory changes at the base, with marked and universal degenerative changes in the nerve cells. The intensity of the inflammatory reaction was similar in the two cases, but the degeneration differed perceptibly in both.

Negri bodies are found in the dog's brain in rabies in the majority of instances. They have not been reported very often in man, though it seems to be accepted that they should be present as frequently in the human brain as in the dog's brain in hydrophobia. Viets reported a case in a human being with typical Negri body formation. A careful search in our case failed to reveal Negri bodies anywhere in the central nervous system. The two cases reported by Schükri and Spatz also showed no Negri bodies. Both of these cases, like ours, followed bites on the face, and were characterized by a very rapid clinical course. In the first case, which followed a wolf bite, death occurred twenty-nine days after the bite and in the second case, fifteen days after the bite. It is possible that the failure to find Negri bodies in the brains in cases of rabies may be related in some way to the acuteness of the disease. In both the cases of Schükri and Spatz and in our own case the course was extremely rapid, and it may be that Negri bodies had no time to form. Cases of rabies without the formation of Negri bodies have been reported by Maas, Abba and Borman, Leutz, J. Koch and Goldberg. Koch reported four such cases.

DISTRIBUTION OF LESIONS AND NATURE OF RABIES

Recent investigations, particularly those of Spatz, Schükri and Spatz, and Seifried and Spatz tend to classify rabies as an encephalitis and to group it with the encephalitides, which include epidemic encephalitis, poliomyelitis, Borna disease in horses, rabies, distemper and chicken plague.

Klarfeld first called attention to the similarity of the pathologic findings in lyssa and epidemic encephalitis. Later Schükri and Spatz studied two cases of rabies chiefly from the standpoint of the distribution of the lesions. They found marked involvement of the midbrain by the inflammatory process, particularly severe in the substantia nigra. The periaqueductal gray matter was rather severely involved, and the nucleus ruber was only mildly infiltrated. In the pons the inflammatory changes were most marked in the tegmentum—in the vicinity of the iter and fourth ventricle. More anteriorly there were isolated areas of infiltration in the floor of the third ventricle, but none in the cortex. The distribution of the inflammation in these two cases, particularly the marked involvement of the midbrain and substantia nigra, in addition to the similarity in the nature of the exudate, led Schükri and Spatz to conclude that rabies and epidemic encephalitis were closely allied and should be placed together in the group of encephalitides. Hassin had previously shown that encephalitis and poliomyelitis are related, the only difference in the two diseases being that in epidemic encephalitis the pathologic changes tended to diminish spinalward, whereas in poliomyelitis they tended to diminish cerebralward. The intensity and distribution of changes in the two diseases may be so similar that they cannot be distinguished. The work of Schükri and Spatz has been confirmed in four cases of rabies by Loewenberg, except that in two of his cases he found marked meningeal infiltrations. More recently, Seifried and Spatz have demonstrated that Borna disease, which is an encephalitis occurring in horses, is similar in all respects to rabies and the other encephalitides, including epidemic encephalitis, rabies, poliomyelitis and other diseases.

According to Seifried and Spatz, the characteristics which distinguish these various encephalitides are: (1) absence of meningeal reaction; (2) predominant involvement of the gray matter; (3) a nonpurulent type of infection, the reaction consisting of lymphocytes, plasma cells and large mononuclear elements; (4) a glial proliferation of a diffuse and focal nature, and (5) a lack of hemorrhages and softenings. Differences between the various members of the group are those of degree; a local meningitis is more common in poliomyelitis than in the other diseases, and leukocytes play a more active rôle in poliomyelitis than in the other encephalitides.

The distribution of the pathologic changes and the inflammation is very much the same in epidemic encephalitis, poliomyelitis, rabies and Borna disease. The inflammatory exudate affects chiefly the gray matter at the base of the brain, involving particularly the colliculi, the periaqueductal gray matter, the substantia nigra and the tegmentum of the pons and medulla, especially the parts just under the fourth ventricle.

In the pons the basis escapes almost entirely. In the medulla the exudate is most active above the inferior olives. Spatz emphasizes the marked involvement of the substantia nigra in rabies, but in our case this nucleus was not particularly affected. In the hypothalamus the portions bordering on the ventricles are most involved. The tuber cinereum and infundibulum are special sites of election. In the forebrain the basal ganglions are most involved by the exudate, especially the caudate nucleus and parts of the thalamus. The changes in the cortex are mild.

In our case the involvement of the spinal cord was pronounced, more even than in poliomyelitis. While the various diseases which are grouped in this class of encephalitides show some differences in distribution, they tend to have characteristics in common which would seem to justify the classification proposed.

From a clinical standpoint the cases here reported bring out several important features: first, the necessity of thoroughly cauterizing the wound, preferably with fuming nitric acid instead of with phenol or other caustic substances. Animal experiments have shown that wounds promptly and thoroughly cauterized with nitric acid are seldom followed by rabies.[1]

The incubation period in the second case was about three weeks, which is considerably below the average of forty days. The shortest incubation period on record is twelve days; the longest, two years. The incubation period tends to be shorter in children than in adults and in cases in which the bite is about the head and face. Both of these factors bear on our case. Recently it has been recommended that more active treatment be given to patients who had bites about the face and head, so as to produce immunity more rapidly. Generally it is considered that at least fourteen days must elapse after completion of the treatment with vaccine before immunity is attained. Therefore, in any case in which the offending dog cannot be traced, thorough cauterization of the wound with fuming nitric acid should be done and antirabic treatment begun at once. If the wound is on the face, the routine treatment should be intensified. The danger of paralysis due to treatment is practically negligible, and of those in whom it develops, about 85 per cent make a complete recovery.

1. In the first case thorough cauterization did not protect the patient from the disease.

TREATMENT OF SECONDARY ANEMIA

WITH SPECIAL REFERENCE TO THE USE OF LIVER EXTRACT INTRAMUSCULARLY

WILLIAM P. MURPHY, M.D.
BOSTON

The comparative value of whole liver, ferrous carbonate, liver extract (fraction G of Cohn) and various combinations of these substances in the treatment of secondary anemia of man was discussed in three previous communications.[1] The present report is concerned with observations as to the relative merit of ferric ammonium citrate, ferric citrate, liver extract for use in secondary anemia (Whipple [2]), solution of liver extract for intramuscular injection [3] and a comparison of these with the substances previously reported on for the treatment of the same type of anemia.

METHODS OF STUDY

Since the methods used in the study of the cases reported here have been similar in most respects to those described previously,[4] a complete description of them will not be repeated. Hemoglobin determinations have been made by means of the Osgood-Haskins [5] modification of the Sahli method. By this method, 100 per cent is equivalent to 13.8 Gm. of hemoglobin per hundred cubic centimeters of blood. This may be considered a low normal level for women. Determinations of the whole

---

From the Medical Clinic of the Peter Bent Brigham Hospital.

This study was aided by a grant from the De Lamar Mobile Fund of the Harvard Medical School.

1. (*a*) Murphy, W. P., and Powers, J. H.: The Value of Liver in the Treatment of Anemia Due to Hemorrhage, Surg., Gynec. & Obst. **48**:480 (April) 1929. (*b*) Murphy, W. P.: Observations on the Treatment of Anemia, ibid. **50**:246 (Jan.) 1930. (*c*) Powers, J. H., and Murphy, W. P.: The Treatment of Secondary Anemia, J. A. M. A. **96**:504 (Feb. 14) 1931.

2. Whipple, G. H.; Robscheit-Robbins, F. S., and Walden, G. B.: Blood Regeneration in Severe Anemia: XXI. A Fraction Potent in Anemia Due to Hemorrhage, Am. J. M. Sc. **179**:628 (May) 1930.

3. Murphy, W. P.: The Parenteral Use of Liver Extract in Pernicious Anemia, J. A. M. A. **98**:1051 (March 26) 1932. This solution was prepared by Lederle Laboratories of New York.

4. Footnote 1*a* and *c*.

5. Osgood, E. E., and Haskins, H. D.: A New Permanent Standard for Estimation of Hemoglobin by the Acid Hematin Method, J. Biol. Chem. **57**:107 (Aug.) 1923.

blood iron,[6] have been continued in these cases as an aid in following the changes in the blood. For reasons which will be discussed in a subsequent paper, the procedure of Wong [7] for the determination of whole blood iron has been used instead of that of Kennedy.[8] By this method the lower limit of normal for women is considered as approximately 43 mg. per hundred cubic centimeters of blood, which is about 6 mg. higher than that previously reported.[9] In order to calculate the hemoglobin from the figure for whole blood iron, each milligram of iron may be considered equal to 0.305 Gm. of hemoglobin. The reticulocytes were counted during the first few days of treatment in several cases, but as the majority of the patients were treated outside of the hospital it was not possible in all. Since the reticulocyte curves are of little value in analyzing the results of treatment of the patients, they will not be shown.

The blood of each patient was examined at weekly intervals when possible, but in the interest of brevity a complete record of the observations is not shown in the tables. Although the final figures may not indicate in each instance an entirely normal state of the blood, an effort has been made to utilize the data for purposes of comparison only to the point at which definite improvement was interrupted for one reason or another. Therefore, in order to compare the results observed in the several groups, it is necessary to take into consideration not only the number of days during which treatment was given but also the level of the hemoglobin and red blood cell counts at the time treatment was begun and the levels to which they improved.

In order to make the record of the effect of the treatment used comparable to that recorded in previous communications, the iron salt was given in some instances in such an amount daily that it would again be the "minimal" effective dose [10] and the actual iron content of the dose used essentially the same as that used previously. Both ferric ammonium citrate and ferric citrate contain about twice as much iron per unit of weight of the salt as is present in pills of ferrous carbonate, U. S. P. That is, a dose of 1 Gm. of ferric ammonium citrate contains

6. Murphy, W. P.; Lynch, R., and Howard, I. M.: The Value of Determinations of the Iron Content of Whole Blood, Arch. Int. Med. **47**:883 (June) 1931. Footnote 1*c*.

7. Wong, S. Y.: Colorimetric Determination of Iron and Hemoglobin in Blood, J. Biol. Chem. **77**:409 (May) 1928.

8. Kennedy, R. P.: The Quantitative Determination of Iron in Tissues, J. Biol. Chem. **74**:385 (Aug.) 1927.

9. Footnote 1*c*.

10. A dose which may reasonably be expected to produce improvement of the blood but which probably does not produce the best results in the majority of patients.

approximately 170 mg. of iron, and of ferric citrate, 186 mg., whereas an essentially comparable amount of iron (173 mg.) is present in pills of ferrous carbonate given in a dosage of 1.8 Gm.

COMMENT ON TABLES AND CASES

The results obtained by each form of treatment are tabulated separately in order to make a comparison of results more satisfactory.

The anemia present in the majority of the patients primarily considered in this paper may be classified as of the chronic chlorotic type or idiopathic hypochromic anemia in which there is a low hemoglobin level with relatively little alteration in the red blood cell count. In a few instances, nutritional factors and chronic loss of blood probably played a rôle in the production of the anemia. Those patients treated with ferrous carbonate referred to in previous papers [4] were, in most instances, anemic owing to chronic hemorrhage. No distinction has been made between the effect of treatment on anemia from the various causes, although those anemic from hemorrhage probably respond to treatment somewhat more readily than do those anemic from other causes.

Observations made during the course of treatment of twelve patients with ferric ammonium citrate and intramuscular injections of solution of liver extract are recorded in tables 1 and 1 *A*. Intramuscular injections only were given to five of these patients for a period before the iron salt was administered and to one other who did not receive iron. The results obtained in these six patients are shown in table 1 *B*.

The amount of solution of liver extract given to each patient varied considerably as shown in tables 1 and 1 *B*. The initial injection was usually the amount of solution derived from 100 to 200 Gm. of liver, and in some instances this dose was repeated within twenty-four hours. Thereafter at intervals varying from one to three weeks during the period of observation, an injection of 3 or 5 cc. prepared from 100 Gm. of liver was given. When iron was used it was given either in solution or capsule [11] in daily doses of 3 Gm. of the salt except in three instances (cases 1, 2 and 5) in which 6 Gm. was used. In case 1 the dose was reduced to 3 Gm. daily after the first three weeks. The solution of liver extract (Lederle) used intramuscularly is iron-free.

The intramuscular injections alone usually resulted in some increase in the red blood cell count with little change in the hemoglobin level. In three instances (cases 7, 11 and X), the hemoglobin increased slightly. A very restricted diet was, no doubt, a contributing factor to the anemia observed in the first of these patients. During the period of observation in which he received only the injections, he received a diet high in iron

11. Prepared by the Lederle Laboratories, New York.

TABLE 1.—*Record of Patients Treated with Solution of Liver Extract Intramuscularly and Ferric Ammonium Citrate by Mouth*

Case	Red Blood Cells, Millions per C.Mm.		Hemoglobin, Gm. per 100 Cc.		Blood Iron, Mg. per 100 Cc.		Liver Solution Injections		Daily Dose of Iron Salt, Gm.	Number of Days Treated
	Initial	Final	Initial	Final	Initial	Final	Date	Amount Injected and Liver from Which Derived		
1	4.49	5.27	7.31	11.87	25.70	44.20	12/12/31	1.2 cc. = 24 Gm.	6	25
							12/13/31	5.0 cc. = 100 Gm.		
	5.27	5.74	11.87	15.59	44.20	49.50	1/ 6/32	3.0 cc. = 100 Gm.		
							1/20/32	3.0 cc. = 100 Gm. †	3	31
							1/27/32	3.0 cc. = 100 Gm. †		
2	2.72	5.51	3.04	14.80	10.37	44.60	4/15/32	6 cc. = 200 Gm.	6	77
							4/18/32	6 cc. = 200 Gm.		
							4/20/32	3 cc. = 100 Gm.		
							4/27/32	3 cc. = 100 Gm.		
							5/ 4/32	3 cc. = 100 Gm.		
							5/18/32	3 cc. = 100 Gm.		
							6/ 1/32	3 cc. = 100 Gm.		
							6/15/32	3 cc. = 100 Gm.		
							6/28/32	3 cc. = 100 Gm.		
3	2.71	5.17	3.04	11.45	12.40	37.30	1/23/32	0.2 cc. = 4 Gm.	3	42
							1/24/32	5.0 cc. = 100 Gm.		
							1/25/32	5.0 cc. = 100 Gm.		
							1/29/32	5.0 cc. = 100 Gm.		
							2/19/32	3.0 cc. = 100 Gm.		
							2/26/32	3.0 cc. = 100 Gm.		
							3/ 4/32	3.0 cc. = 100 Gm.		
4*	4.86	6.05	7.73	15.39	29.40	42.70	3/ 2/32	6 cc. = 200 Gm.	3	21
							3/16/32	3 cc. = 100 Gm.		
							3/23/32	3 cc. = 100 Gm.		
5	5.19	5.65	8.97	14.80	.....	.....	4/21/32	3 cc. = 100 Gm.	6	63
							4/28/32	3 cc. = 100 Gm.		
							5/ 5/32	3 cc. = 100 Gm.		
							5/19/32	3 cc. = 100 Gm.		
							5/27/32	3 cc. = 100 Gm.		
6	4.72	5.38	8.42	11.73	29.20	37.70	5/17/32	6 cc. = 200 Gm.	3	35
							5/25/32	3 cc. = 100 Gm.		
							6/ 1/32	3 cc. = 100 Gm.		
							6/ 8/32	3 cc. = 100 Gm.		
							6/15/32	3 cc. = 100 Gm.		
							6/22/32	3 cc. = 100 Gm.		
7*	4.17	4.83	10.07	13.66	40.30	42.00	12/28/31	5 cc. = 100 Gm.	3	21
8	4.83	5.39	8.28	12.14	.....	.....	5/18/32	3 cc. = 100 Gm.	4	21
							5/21/32	6 cc. = 200 Gm.		
							5/27/32	3 cc. = 100 Gm.		
							6/ 6/32	3 cc. = 100 Gm.		
							6/13/32	3 cc. = 100 Gm.		
9*	3.91	4.88	4.55	12.76	18.00	41.80	5/24/32	3 cc. = 100 Gm. †	3	63
							6/ 1/32	3 cc. = 100 Gm. †		
							6/22/32	3 cc. = 100 Gm. †	0	
							7/ 6/32	3 cc. = 100 Gm. †		
							7/13/32	3 cc. = 100 Gm.	3	
							7/20/32	3 cc. = 100 Gm.		
							7/27/32	3 cc. = 100 Gm.		
10*	5.00	5.53	5.24	12.42	19.10	40.10	6/15/32	3 cc. = 100 Gm.	3	49
							6/29/32	3 cc. = 100 Gm.		
							7/ 6/32	3 cc. = 100 Gm.		
							7/13/32	3 cc. = 100 Gm.		
							7/27/32	3 cc. = 100 Gm.		
							8/ 3/32	3 cc. = 100 Gm.		
11*	6.14	6.25	10.21	13.11	35.70	41.15	7/ 6/32	3 cc. = 100 Gm.	3	35
							7/13/32	3 cc. = 100 Gm.		
							7/20/32	3 cc. = 100 Gm.		
							7/27/32	3 cc. = 100 Gm.		
							8/ 3/32	3 cc. = 100 Gm.		
12	2.67	5.16	4.97	11.73	18.05	39.20	6/23/32	6 cc. = 200 Gm.	1.84	49
							6/29/32	3 cc. = 100 Gm.		
							7/ 6/32	3 cc. = 100 Gm.		
							7/13/32	3 cc. = 100 Gm.		
							7/20/32	3 cc. = 100 Gm.		
							7/27/32	3 cc. = 100 Gm.		
							8/ 3/32	3 cc. = 100 Gm.		

* See table 1B for the results of treatment with solution of liver extract alone. The red blood cell count has been increased in cases 4, 7, 9 and 11 by the previous treatment.

† Pills of ferrous carbonate, U. S. P.

content (but without liver), which may in part account for the increase in hemoglobin. The third of the three patients entered the hospital with a generalized skin eruption of unexplained origin and an anemia. Following the injections, the red blood cell count increased, the eruption cleared up and the patient's general condition improved strikingly up to the time of discharge from the hospital. Further follow-up treatment was not possible.

Improvement in the patients treated with injections of solution of liver extract and iron by mouth has been unusually rapid (tables 1 and 1 *A*),[11a] and in the majority the final red blood cell count, hemo-

TABLE 1*A*.—*Detailed Record of Changes in the Hemoglobin in Patients*

	Initial			Increase in Hemo											
Case	Red Blood Cells	Hemoglobin	Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day
1	4.49†	7.31	25.70	....	.....	1.52	138.2	3.87	215.0	4.56	182.5	4.28	134.0	7.04	180.5
2	2.72	3.04	10.37	0.41	58.5	2.07	147.6	4.83	230.0	....	.....	7.47	213.0	....	.....
3	2.71	3.04	12.40	1.10	157.0	3.17	226.2	3.86	184.3	7.17	256.0	7.59	216.8	8.14	209.2
4	4.86	7.73	29.40	2.48	354.2	4.00	286.0	5.66	269.5	....	.....	....	.....	....	.....
5	5.19	8.97	.....	....	.....	....	.....	....	.....	4.83	172.5	....	.....	....	.....
6	4.72	8.42	29.20	0.41	58.5	....	.....	2.90	138.2	4.00	142.9	3.31	94.6	....	.....
7	4.17	10.07	.....	1.25	178.5	1.80	128.4	3.59	171.0	....	.....	....	.....	....	.....
8	4.83	8.28	.....	....	.....	1.66	118.7‡	3.86	184.3	....	.....	....	.....	....	.....
9	3.91	4.55	18.00	1.25	178.5	3.73	259.1	4.70	222.9	5.25	187.5	5.94	169.5	6.35	151.4
10	5.00	5.24	19.10	....	.....	1.38	98.5	2.90	138.1	3.45	123.2	....	.....	6.72	160.0
11	6.14	10.21	35.70	1.24	177.1	0.55	39.3	....	.....	2.35§	83.9	2.90	82.8	....	.....
12	2.67	4.97	18.05	1.38	197.1	2.62	187.1	5.24	249.1	6.03	215.5	5.94	169.6	6.35	151.2
Averages.....				1.19	170.0	2.24	162.9	4.14	200.2	4.71	170.5	5.35	154.3	6.92	168.6

* The gain in hemoglobin at intervals of seven days is shown in grams; the gain per day, in milligrams.
† The calculations were actually based on intervals three days shorter than listed.
‡ No iron was given for one week.
§ No iron was given for two weeks.

globin and whole blood iron levels have been higher than in the other groups reported. One patient (case 3) had a complicating mild arthritis with cholecystitis and cholelithiasis. Another patient (case 9) improved satisfactorily in spite of the fact that she took care, practically night and day, of four children very ill with whooping cough.

In tables 2 and 2 *A* are recorded observations obtained in following the effect on the blood of sixteen patients treated with ferric ammonium citrate. The first eight patients received 1 Gm. of the salt daily, whereas the others received 2, 3 or 6 Gm. daily.

11a. Seven other patients have been treated by this method since the tables were prepared, so the results are not recorded therein. Improvement in these seven has been more striking than in the twelve cases the results of which are recorded in tables 1 and 1 *A*.

One patient of this group (case 17) had a basal metabolic rate of minus 18 per cent and for twenty-three days before beginning iron therapy received daily 0.130 Gm. of thyroid substance. Although the basal metabolic rate had increased to minus 5 per cent and she felt better, there had been little change in the blood. Thyroid medication was continued along with the iron. Prior to starting iron treatment, another patient (case 19) received daily for forty-two days 120 Gm. of "yellow" bone marrow preserved by freezing. During this period of treatment, the red blood cell count increased from 2,410,000 to 2,970,000 and the hemoglobin from 4.28 to 4.83 Gm. per hundred cubic centi-

Treated with Liver Solution and Ferric Ammonium Citrate as in Table 1

globin *										Final			Total Gain		
49 Days	Per Day	56 Days	Per Day	63 Days	Per Day	70 Days	Per Day	77 Days	Per Day	Red Blood Cells	Hemoglobin	Blood Iron	Red Blood Cells	Hemoglobin	Blood Iron
7.33	172.0	8.28	156.4	....	.....	....	.....	....	.....	5.74	15.59	49.50	1.25	8.28	23.80
9.79	199.0	....	.. ..	10.48	166.3	....	.....	11.86	154.0	5.51	14.90	44.60	2.79	11.86	34.23
....	.....	....	..	....	.....	....	.....	....	.....	5.17	11.45	37.30	2.46	8.14	24.90
....	.....	....	.....	....	.....	....	.....	....	.....	6.05	13.39	42.70	1.19	5.66	13.30
....	.....	....	.....	5.93	94.2	....	.....	....	.....	5.65	14.90	.....	0.46	5.93	.....
....	.....	....	.....	....	.....	....	.....	....	.....	5.38	11.73	37.70	0.66	3.31	8.50
....	.....	....	.....	....	.....	....	.....	....	.....	4.83	13.66	42.00	0.66	3.59	.....
....	.....	....	.....	....	.....	....	.....	....	.....	5.59	12.14	.....	0.76	3.86	.....
6.638	135.4	6.82	121.8	8.21	130.3	....	.....	....	.....	4.88	12.76	41.80	0.97	8.21	23.80
7.18	146.5	....	.....	....	.....	....	.....	....	.....	5.53	12.42	40.10	0.53	7.18	21.00
....	.....	....	.....	....	.....	....	.....	....	.....	6.25	13.11	41.15	0.11	2.90	5.45
6.76	138.0	....	.....	....	.....	....	.....	....	.....	5.16	11.73	39.20	2.49	6.76	21.15
7.02	155.5	7.55	134.8	8.21	130.4	....	.....	11.86	154.0	....	.....	.....	....	6.32	19.57

meters of blood. In a similar period of time, with 1 Gm. of ferric ammonium citrate the red blood cell count rose from 2,970,000 to 4,150,000 and the hemoglobin level from 4.83 to 8.69 Gm. per hundred cubic centimeters of blood. Subsequent improvement in this patient did not occur as rapidly as in most of the others, no doubt partly because of her inability to secure proper food after her discharge from the hospital. The same factor probably was an important contributing cause of the anemia. The anti-anemia diet which she received for seventy days in the hospital may have aided in her improvement. The patient in case 20 was given for thirty-seven days six teaspoonfuls daily of a colloidal iron compound. No definite change in the blood occurred, whereas with 1 Gm. of ferric ammonium citrate given daily for thirty-five days the red blood cell count rose from 4,290,000 to 4,960,000 and the hemo-

globin from 5.24 to 8.28 Gm. per hundred cubic centimeters of blood. One other patient received the same preparation without improvement but later failed to carry out treatment with another form of iron so the results are not recorded. Two patients (cases 24 and 25) received intravenous injections of colloidal iron hydroxide, averaging 3 cc. daily (each 3 cc. containing 4 mg. of iron) before oral treatment was begun, and the figures showing the results of this treatment are recorded in tables 3 and 3 *A*. One of these (case 24) was observed for seventy days during this form of treatment and in addition received several

TABLE 1*B*.—*Record of Patients Treated with Solution of Liver Extract Intramuscularly without Iron*

Case	Red Blood Cells, Millions per C.Mm.		Hemoglobin, Gm. per 100 Cc.		Blood Iron, Mg. per 100 Cc.		Liver Solution Injections		Number of Days
	Initial	Final	Initial	Final	Initial	Final	Date	Amount Injected and Liver from Which Derived	
4	4.40	4.86	8.97	7.73	31.70	24.90	2/ 3/32 2/ 4/32	6 cc. = 200 Gm. 6 cc. = 200 Gm.	28
7	3.25	4.17	8.14	10.07	30.03	40.30	11/18/31 11/19/31 11/20/31 12/ 8/31 12/ 9/31	0.2 cc. = 4 Gm. 10.0 cc. = 200 Gm. 10.0 cc. = 200 Gm. 10.0 cc. = 200 Gm. 4.0 cc. = 80 Gm.	40
9	3.37	3.91	5.93	4.55	17.61	18.00	4/22/32 4/27/32 5/24/32	6.0 cc. = 200 Gm. 6.0 cc. = 200 Gm. 3.0 cc. = 100 Gm.	32
10	5.37	5.00	5.38	5.24	21.10	19.10	5/19/32 5/20/32 5/26/32 6/ 1/32 6/ 8/32 6/15/32	6 cc. = 200 Gm. 6 cc. = 200 Gm. 3 cc. = 100 Gm. 3 cc. = 100 Gm. 3 cc. = 100 Gm. 3 cc. = 100 Gm.	27
11	5.56	6.14	9.80	10.21	36.50	35.70	5/31/32 6/ 8/32 6/15/32 6/22/32 6/29/32 7/ 6/32	3 cc. = 100 Gm. 3 cc. = 100 Gm. 3 cc. = 100 Gm. 3 cc. = 100 Gm. 3 cc. = 100 Gm. 3 cc. = 100 Gm.	37
X	3.79	4.86	10.21	11.45	35.70	37.60	2/12/32 2/13/32	6 cc. = 200 Gm. 6 cc. = 200 Gm.	32

intravenous injections of a copper preparation during the last sixteen days. This patient had lived for several months on a diet composed essentially of crackers or bread and tea. She received an adequate diet for eighteen days in the hospital and was able to continue it satisfactorily during her entire period of treatment. This fact must be considered in evaluating the effect of the iron medications used.

The patient in case 23 received some iron during the course of pregnancy, but the observations recorded begin with intensive treatment one week post partum.

The patients in cases 13 and 14 were first treated with a liver fraction for use in secondary anemia (Whipple).[3] The results obtained with

this treatment are shown in tables 3 and 3 *A*, together with the results obtained in another patient (case 34) treated by the same means.

The results of treatment of six patients with varying doses of ferric citrate are shown in tables 4 and 4 *A*. The patient in case 31 had a severe cold at the onset of treatment, which continued for two weeks and recurred again in three weeks. Improvement as shown in the table

TABLE 2.—*Record of Patients Treated with Ferric Ammonium Citrate*

Case	Red Blood Cells, Millions per C.Mm.		Hemoglobin, Gm. per 100 Cc.		Blood Iron, Mg. per 100 Cc.		Daily Dose Iron Salt, Gm.	Number of Days Treated	Comment
	Initial	Final	Initial	Final	Initial	Final			
13	4.74	5.07	7.90	11.38	25.90	37.30	0.9*	70	See tables 3 and 3A, case 13, for previous treatment; final red blood cell count recorded was made at end of 35 day period
14	4.62	4.87	11.06	14.39	36.23	47.10	1.0*	70	See tables 3 and 3A, case 14, for previous treatment
15	3.72	4.93	6.49	8.83	.....	.....	1.0†	49	
16	2.37	4.94	4.42	11.59	16.47	44.50	1.0†	91	Profuse catamenial flow last two weeks
17	3.56	4.77	7.18	14.08	24.30	44.20	1.0†	84	Thyroid substance, 0.13 Gm. daily
18	3.91	5.33	4.83	13.52	18.18	42.50	1.0†	91	
19	2.97	5.14	4.83	11.73	15.75	36.60	1.0†	105	Inadequate diet before and during treatment; 120 Gm. yellow bone marrow daily for 42 days previously
20	4.29	5.51	5.24	13.25	20.00	46.70	1.0†	133	See text regarding previous iron treatment
21	4.56	4.92	11.87	14.49	42.30	46.09	2.0†	56	
22	4.39	5.06	8.00	13.25	26.70	42.70	3.0*	63	
23	4.72	5.10	8.97	13.52	27.50	43.40	3.0*	70	Record starts one week post partum
24	4.68	5.38	7.87	13.25	24.50	43.80	3.0*	42	See tables 3 and 3A for previous intravenous therapy
25	4.59	5.08	9.52	12.83	36.49	40.48	3.0*	35	See tables 3 and 3A for previous intravenous therapy
26	4.40	5.39	5.52	11.04	17.77	36.50	6.0†	49	
27	3.85	4.43	10.63	13.66	34.70	44.40	6.0†	42	
28	5.38	5.35	11.59	14.08	38.90	45.00	6.0*	56	

* Ferric ammonium citrate given in capsule form as prepared by Lederle Laboratories.
† Ferric ammonium citrate given in solution.

was probably definitely retarded during this time, but after an interval of time had elapsed and the infection had cleared up improvement took place more rapidly, the hemoglobin increasing in five weeks by 2 Gm. or an average of 54 mg. per day. These figures are not shown in the table. One other patient treated with ferric citrate but for whom the results are not shown in the table improved very slowly during the time that she had a chronic sinus infection with frequent acute exacerbations.

For purposes of comparison, there is a record of the results following the use of pills of ferrous carbonate shown in table 5 *A*. In this table are also included the results in patients who received liver extract

(fraction G of Cohn) with iron, which was shown previously to be ineffective in the production of hemoglobin and is therefore not taken into account. In table 6 *A* are similarly recorded the observations of the results obtained with ferrous carbonate and whole liver. Some of the data contained in tables 5 *A* and 6 *A* have been shown in different form in previous communications.[4] The minimal doses of ferric

TABLE 2*A*.—*Detailed Record of Changes in the Hemoglobin of*

Case	Initial: Red Blood Cells	Initial: Hemoglobin	Initial: Blood Iron	Increase in Hemoglobin: 7 Days	14 Days	21 Days	28 Days	35 Days	42 Days	49 Days	56 Days	63 Days	70 Days
13	4.74	7.90	25.90	1.06	0.55	1.10	3.30	3.48	.....	.....	.....	.....	.....
Per day				151.5	39.9	52.4	117.9	99.4	.....	.....	.....	.....	.....
14	4.62	11.06	36.23	1.34	0.06	—0.68	.....	.....	.....	.....	2.54	.....	.....
Per day				191.4	4.3	—32.0	.....	.....	.....	.....	45.4	.....	47.2
15	3.72	6.49	.....	1.10	1.65	2.48	.....	.....	0.56	2.34	.....	.....	.....
Per day				157.1	117.8	118.2	.....	.....	13.3	47.7	.....	.....	.....
16	2.37	4.42	16.42	0.69	2.34	2.07	3.45	3.68	3.82	5.38	4.69	5.65	5.18
Per day				98.6	167.1	98.5	123.2	105.1	91.0	109.7	83.6	89.4	84.7
17	3.56	7.18	24.30	0.41	0.27	2.89	3.58	4.00	4.83	4.83	4.41	5.65	4.96
Per day				59.6	19.39	137.5	128.0	114.3	115.1	98.6	78.7	89.4	70.8
18	3.91	4.83	18.18	0.69	2.48	3.04	2.76	3.45	5.93	4.69	5.80	6.49	6.35
Per day				98.6	177.2	144.8	98.6	98.5	141.1	95.7	103.6	103.0	90.7
19	2.97	4.83	15.75	0.41	.....	1.38	2.48	.....	3.86	4.40	4.00	.....	4.32
Per day				59.6	.....	65.7	88.6	.....	91.9	.....	71.4	.....	63.0
20	4.29	5.24	20.00	—0.27	1.25	1.11	3.87	3.04	.....	.....	4.42	4.83	5.72
Per day				—38.6	98.4	52.7	138.3	87.1	.....	.....	79.0	76.8	78.3
21	4.56	11.87	.....	.....	1.24	.....	.....	.....	0.83	1.65	2.62	.....	.....
Per day				.....	88.5	.....	.....	.....	19.7	36.8	46.8	.....	.....
22	4.39	8.00	26.70	0.69	3.04	3.50	3.04	4.83	4.70	4.28	4.70	5.25	.....
Per day				98.6	217.5	171.0	108.6	138.0	111.9	87.3	84.0	83.4	.....
23	4.72	8.97	27.30	.....	.....	2.62	2.62	.....	.....	2.99	.....	3.73	4.57
Per day				.....	.....	124.8	93.6	.....	.....	61.0	.....	59.2	65.3
24	4.68	7.87	24.50	0.82	2.33	4.41	4.93	5.52	5.38	.....	.....	.....	.....
Per day				117.2	166.2	209.9	176.0	158.0	128.1	.....	.....	.....	.....
25	4.59	9.52	.....	.....	.....	.....	.....	3.31	.....	.....	.....	.....	.....
Per day				.....	.....	.....	.....	94.5	.....	.....	.....	.....	.....
26	4.40	5.52	17.77	.....	0.69	.....	2.35	2.76	4.83	5.52	.....	.....	.....
Per day				.....	49.3	.....	93.9	78.9	115.1	112.7	.....	.....	.....
27	3.85	10.63	34.70	.....	.....	1.33	2.83	.....	3.03	.....	.....	.....	.....
Per day				.....	.....	63.4	101.1	.....	72.1	.....	.....	.....	.....
28	5.38	11.50	38.90	0.97	0.97	1.80	1.93	2.35	2.38	2.26	2.49	.....	.....
Per day				138.6	69.3	85.6	68.9	67.1	56.7	46.1	44.4	.....	.....
Averages				0.72	1.41	2.09	3.10	3.64	3.65	3.83	3.96	5.26	5.00
Per day				102.9	101.2	99.4	111.4	104.1	93.1	77.3	70.6	83.5	71.9

[a] The gain in hemoglobin at intervals of seven days is shown in grams; the gain per day, in milligrams.

ammonium citrate appear to be distinctly more effective than similar doses of ferric citrate and about the same as pills of ferrous carbonate, when given in doses containing essentially the same amount of iron.

Although improvement in the blood was more satisfactory in those patients receiving the larger doses (3 Gm. daily of ferric ammonium citrate) than in those receiving the smaller ones (1 Gm. daily of ferric ammonium citrate), the difference in effect is not directly proportional to the amount of iron ingested.

In a previous paper the lack of effectiveness of liver extract (Cohn fraction G) [12] in the treatment of secondary anemia in man was noted. Whipple and his associates [3] have prepared a liver fraction which they have found to be effective in producing hemoglobin when given by mouth to dogs made anemic by bleeding. Three patients were treated by means of such a liver fraction without added iron, and the results

Patients Treated with Ferric Ammonium Citrate as in Table 2

Hemoglobin*									Final			Total Gain		
77 Days	84 Days	91 Days	98 Days	105 Days	112 Days	119 Days	126 Days	133 Days	Red Blood Cells	Hemoglobin	Blood Iron	Red Blood Cells	Hemoglobin	Blood Iron
.....	.....	.....	.....	.....	.....	.....	.....	.....	5.07	11.38	37.30	0.33	3.48	11.40
.....	.....	.....	.....	.....	.....	.....	.....	.....						
.....	.....	.....	.....	.....	.....	.....	.....	.....	4.87	14.39	47.10	0.25	3.33	10.87
.....	.....	.....	.....	.....	.....	.....	.....	.....						
.....	.....	.....	.....	.....	.....	.....	.....	.....	4.93	8.83	.....	1.21	2.34	.....
.....	.....	.....	.....	.....	.....	.....	.....	.....						
5.90	6.48	7.17	.....	.....	.....	.....	.....	.....	4.94	11.59	44.50	2.57	7.17	28.03
77.0	77.1	78.7	.....	.....	.....	.....	.....	.....						
5.67	6.90	.....	.....	.....	.....	.....	.....	.....	4.77	14.08	44.20	1.21	6.90	19.90
73.4	82.1	.....	.....	.....	.....	.....	.....	.....						
6.21	7.45	8.69	.....	.....	.....	.....	.....	.....	5.33	13.52	42.50	1.42	8.69	24.32
80.7	88.7	95.4	.....	.....	.....	.....	.....	.....						
4.69	.....	4.83	.....	6.90	.....	.....	.....	.....	5.14	11.73	36.6	2.17	6.90	20.85
60.9	.....	53.1	.....	65.7	.....	.....	.....	.....						
....	6.08	.....	7.32	8.15	7.73	7.59	.....	8.01	5.51	13.25	46.70	1.22	8.01	26.70
....	72.3	.....	74.6	77.5	69.0	63.7	.....	60.2						
.....	.....	.....	.....	.....	.....	.....	.....	.....	4.92	14.49	.....	0.96	2.62	.....
.....	.....	.....	.....	.....	.....	.....	.....	.....						
.....	.....	.....	.....	.....	.....	.....	.....	.....	5.06	13.25	42.70	0.67	5.25	16.09
.....	.....	.....	.....	.....	.....	.....	.....	.....						
.....	.....	.....	.....	.....	.....	.....	.....	.....	5.10	13.52	43.40	0.38	4.55	15.09
.....	.....	.....	.....	.....	.....	.....	.....	.....						
.....	.....	.....	.....	.....	.....	.....	.....	.....	5.38	13.25	43.80	0.70	5.38	19.30
.....	.....	.....	.....	.....	.....	.....	.....	.....						
.....	.....	.....	.....	.....	.....	.....	.....	.....	5.08	12.83	.....	0.40	3.31	.....
.....	.....	.....	.....	.....	.....	.....	.....	.....						
.....	.....	.....	.....	.....	.....	.....	.....	.....	5.39	11.04	36.50	0.99	5.52	18.73
.....	.....	.....	.....	.....	.....	.....	.....	.....						
.....	.....	.....	.....	.....	.....	.....	.....	.....	4.43	13.66	44.40	0.58	3.03	9.70
.....	.....	.....	.....	.....	.....	.....	.....	.....						
.....	.....	.....	.....	.....	.....	.....	.....	.....	5.35	14.08	45.0	−0.03	2.49	5.50
.....	.....	.....	.....	.....	.....	.....	.....	.....						
5.92	6.72	6.89	7.32	7.53	7.73	7.59	.....	8.01	....	.....	.....	....	5.64	17.48
75.0	80.0	75.7	74.6	71.6	69.0	63.7	.....	60.2						

are recorded in tables 3 and 3 *A*. In one of the patients (case 34) improvement in the blood occurred at a rate which might be expected with the use of a minimal dose of an iron salt. Very slight improvement was noted in the other two (cases 13 and 14). The liver extract used in case 34, tested for its iron content, was found to contain approxi-

12. Cohn, E. J.; Minot, G. R.; Fulton, J. F.; Ulrichs, H. F.; Sargent, F. C.; Weare, J. H., and Murphy, W. P.: The Nature of the Material in Liver Effective in Pernicious Anemia, J. Biol. Chem. **74**:69 (July) 1927.

mately 110 mg. of iron in the daily dose used. That used in cases 13 and 14 contained only about 9 mg. in the daily dose. The observed effect of these extracts in the treatment of human secondary anemia is probably entirely dependent on the iron content of the extract. Similar conclusions have been reached by Cheney and Niemand.[13]

In tables 3 and 3 *A* are recorded also the results obtained in two patients following the intravenous injection of iron hydroxide. Both patients improved to some extent, although in one instance the alteration in diet may have been largely responsible for the improvement noted (case 24). Further treatment by injections of iron and of copper had to be omitted because of the occurrence of reactions following the injection. The reactions consisted of a rush of heat to the face with flushing and dizziness lasting for a few minutes, followed by

TABLE 3.—*Record of Patients Treated with Secondary Anemia Liver Fraction (Whipple) or Intravenous Injections of Iron Hydroxide*

	Red Blood Cells, Millions per C.Mm.		Hemoglobin, Gm. per 100 Cc.		Blood Iron, Mg. per 100 Cc.		Number of Days	
Case*	Initial	Final	Initial	Final	Initial	Final	Treated	Treatment
13	4.76	4.74	8.94	7.90	29.24	25.90	56	Whipple fraction prepared from 240 Gm. liver daily by mouth
14	4.99	4.62	10.38	11.06	34.01	36.23	70	Whipple fraction prepared from 200 Gm. liver daily by mouth
34	4.10	4.67	9.11	12.42	34.50	43.80	49	Whipple fraction prepared from 1,000 Gm. liver daily by mouth
24	2.14	4.68	4.55	7.87	17.60	24.50	77	$FeOH_2$,† 3 cc. daily intravenously
25	4.63	4.59	9.25	9.52	34.20	36.49	28	$FeOH_2$, 3 cc. daily intravenously

* The patients in cases 13, 14, 24 and 25 were later treated with ferric ammonium citrate. See tables 2 and 2A.

† This patient received injections of copper also during last sixteen days of treatment.

faintness. The effects of subsequent treatment of these two patients with ferric ammonium citrate are shown in tables 2 and 2 *A* (cases 24 and 25). Although there would appear to be some value in iron administered parenterally, it probably has no advantage over that taken by mouth, especially if one considers the number of injections used and the inconvenience and expense to the patient. Difficulty in the ingestion of a sufficient amount of iron is rare indeed.

Several miscellaneous substances prepared for use in the treatment of anemia were each tried in one or two cases with little or no effect when compared to that subsequently obtained with the use of a simple iron salt. In view of the satisfactory results which may be obtained with the simple iron salts in even moderate doses and the striking results observed with the use of an iron salt together with the intramuscular

13. Cheney, G., and Niemand, F.: The Treatment of Secondary Anemia with "Secondary Anemia Liver Extract" and Iron, Am. J. M. Sc. **184**:314 (Sept.) 1932.

injection of liver solution, there would seem to be little indication for the use of complicated preparations, many of which are distinctly more expensive and more difficult to take. With the use of the simple iron salts which are generally contaminated with copper and the ready availability of copper in the diet as generally advised in the treatment of anemia,[14] the question of the need for added copper in the treatment of anemia of the adult is of academic rather than of practical importance.

A condensed summary of the various forms of treatment is also presented in charts 1, 2 and 3. Since there was considerable variation in the different periods of treatment, in order to make a fair comparison all have been considered for an interval of sixty-three days. In the evaluation of the various forms of therapy, especially when comparing

Chart 1

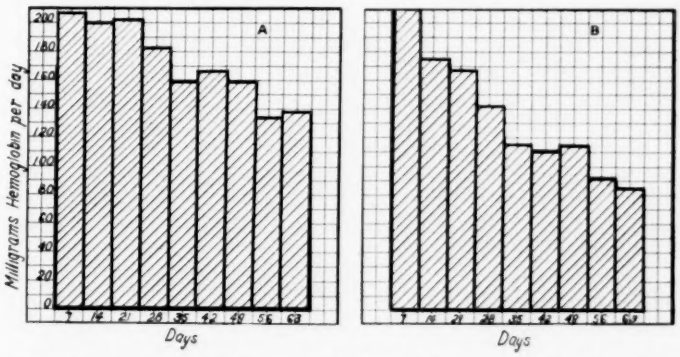


Chart 1.—In *A* are given the averages for nineteen patients treated with solution of liver extract (Lederle) intramuscularly and ferric ammonium citrate by mouth (table 1 *A*). Seven of this group were treated after the paper was presented for publication, and data showing the rate of improvement in them are not recorded in tables 1 and 1 *A*. In *B* are given the averages for seven patients treated with whole liver and ferrous carbonate (table 6 *A*). Each vertical column in the charts represents the total average daily gain of hemoglobin in the patients of each group observed at seven day intervals.

the effects obtained with whole liver and iron (ferrous carbonate) with those obtained with intramuscular injection of solution of liver extract (Lederle) and iron (ferric ammonium citrate), it should be noted that the average ingestion of whole liver for sixty-three days was approxi-

14. Minot, G. R., and Murphy, W. P.: Treatment of Pernicious Anemia by a Special Diet, J. A. M. A. **87**:470 (Aug. 14) 1926. Murphy, W. P., and Minot, G. R.: A Special Diet for Patients with Pernicious Anemia, Boston M. & S. J. **195**:410 (Aug. 26) 1926.

mately 14,000 Gm. (32 pounds), whereas the maximum amount of solution of liver extract injected over the same period represented the material obtained from not more than 1,000 Gm. (2.2 pounds) of liver (ten 3 cc. vials of liver extract). Since the clinical results obtained with ferrous carbonate compare favorably with those obtained with ferric ammonium citrate when equivalents of iron are used, and since the majority of the patients receiving the solution of liver extract belong to the chronic chlorotic type and probably respond less readily to treatment than do those with anemia resulting from chronic hemorrhage as in the group receiving whole liver, the superiority of the combination of intramuscular injections of solutions of liver extract together with ferric ammonium citrate administered by mouth is demonstrated.

TABLE 3A.—*Detailed Record of Changes in the Hemoglobin of Patients Treated with Secondary Anemia*

	Initial			Increase in Hemo										
Case†	Red Blood Cells	Hemoglobin	Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day
13	4.76	8.94	29.24	—1.10	—157.2	—0.56	—40.0	0.51	24.3	0.03	1.0	....	.....	....	.....
14	4.99	10.38	34.01	....	.....	—0.22	—15.7	—0.07	—3.3	1.15	41.0	1.12	32.0	0.32	7.6
34	4.10	9.11	34.50	1.10	157.2	1.65	117.9	....	.....	1.65	59.0	....	.....	2.21	52.6
24	2.14	4.55	17.60	0.42	60.0	0.85	60.7	0.85	40.4	1.52	54.3	2.21	63.2	1.25	29.7
25	4.63	9.25	34.20	1.38	197.1	....	.....	1.65	78.5	0.27	9.64	....	.....	....	.....

† The gain in hemoglobin at intervals of seven days is shown in grams, the gain per day, in milligrams.
‡ The patients in cases 13, 14 and 34 were treated with secondary anemia liver fraction (Whipple); those in cases 24 and 25, with iron hydroxide intravenously.

CLINICAL RESULTS

When considered as to speed of recovery, the general clinical effect observed and the increase in blood, improvement has been most striking in that group of patients who received intramuscular injections of the solution of liver extract (Lederle) together with ferric ammonium citrate by mouth. The rapidity of improvement noted in this group may be best illustrated by means of a comparison (table 7) of the effect of the various forms of treatment used. In this table are recorded the averages of the total gain in hemoglobin in grams and whole blood iron in milligrams in the patients of each group as shown in the six preceding tables called *A*. In the last column is also recorded the average daily gain in hemoglobin, expressed in milligrams. Each of the figures in this group was obtained by dividing the total average gain for each group by the total number of days during which the patients of the same group were observed. The varied results indicated by a comparison of these figures are borne out by all of the data obtained in studying the various groups. The average daily gain of 153.2 mg. of hemoglobin per

day in the group treated with the solution of liver extract intramuscularly together with ferric ammonium citrate by mouth represents almost twice as great an average daily gain as was observed with any other form of treatment. There are no figures available from similar observations in man with which these may be compared. Strauss and Castle [15] treated the anemia of pregnancy with "large doses" of iron (ferric ammonium citrate) and found a daily average increase in hemoglobin of 0.65 per cent, or 101.4 mg. calculated on the basis of 15.6 Gm. of hemoglobin, which is equivalent to 100 per cent by the method used (Sahli [16]). Using full doses of liver or kidney together with iron in dogs made anemic by bleeding, Whipple [17] recorded the production of 140 Gm. of hemoglobin in a fourteen day period. No such gains as

Liver Fraction (Whipple) or Intravenous Injections of Iron Hydroxide as in Table 3

globin 9										Final			Total Gain		
49 Days	Per Day	56 Days	Per Day	63 Days	Per Day	70 Days	Per Day	77 Days	Per Day	Red Blood Cells	Hemoglobin	Blood Iron	Red Blood Cells	Hemoglobin	Blood Iron
....	.....	−1.04	−18.5	....	.....	....	.....	....	.....	4.74	7.90	25.90	−0.02	−1.04	−3.34
1.06	21.6	0.89	15.9	0.81	12.8	0.68	9.7	....	.....	4.62	11.06	36.23	−0.37	0.68	2.22
3.31	67.6	....	.....	....	.....	....	.....	....	.....	4.67	12.42	43.80	0.57	3.31	9.30
....	.....	1.25	22.16	1.38	21.9	3.04	43.4	3.32	43.1	4.68	7.87	24.50	2.54	3.32	6.90
....	.....	....	.....	....	.....	....	.....	....	.....	4.59	9.52	36.49	−0.04	0.27	2.29

this have been made, even for short periods of time, in the patients treated by the various means herein discussed.

Even in those patients who, at least for a time, received only the intramuscular injections of the liver extract, subjective improvement was notable in spite of little or no increase in the hemoglobin level. The different amounts of iron ingested, so far as the dose used is concerned, seems not to have influenced the rate of improvement considerably and can hardly be considered responsible for the difference in the improvement noted in this group as compared with the group treated only with ferric ammonium citrate. As has been observed following the use of liver extract parenterally in the treatment of pernicious anemia,[3] a striking increase in appetite was noted following the injection of the liver solution and a gain of weight occurred in almost every instance.

15. Strauss, M. B., and Castle, W. B.: The Etiology and Treatment of Anemia of Pregnancy, Lancet **1**:1198 (June 4) 1932.

16. Castle: Personal communication.

17. Whipple, G. H.: Experimental Anemias, Diet Factors and Related Pathologic Changes of Human Anemias, J A. M. A. **91**:863 (Sept. 22) 1928.

Indeed, it is difficult to picture the striking changes which have occurred during the course of treatment as just outlined. A description of the change which occurred during the course of treatment of a patient by a physician in Boston and not included in the table will give one an idea of the result to be expected.[18]

REPORT OF CASE

A widow, aged 71, anemic for many years, was visited in April because of pallor, weakness and a severe productive cough. There had been bleeding from hemorrhoids for many years in the past, but none had occurred for several years. She was confined to bed, but there was no fever. An examination showed marked pallor, emaciation, generalized arteriosclerosis and moderate enlargement of the heart. The hemoglobin was 35 per cent (Tallqvist); red blood cell count, 2,568,000, and white blood cell count, 3,800. The red blood cells were small generally, with marked variation in shape. On April 18, treatment with 3 Gm. of ferric ammonium

TABLE 4.—*Record of Patients Treated with Ferric Citrate*

	Red Blood Cells, Millions per C.Mm.		Hemoglobin, Gm. per 100 Cc.		Blood Iron, Mg. per 100 Cc.		Daily Dose Iron Salt, Gm.	Number of Days Treated	
Case	Initial	Final	Initial	Final	Initial	Final			Comment
29	3.92	4.92	6.76	11.73	23.81	39.60	1*	49	Started day after operation; salpingoophorectomy
30	4.81	4.80	10.63	11.73	32.89	37.31	1*	56	
31	4.64	5.36	7.87	11.59	27.60	35.20	1*	91	Frequent colds during early part of treatment
32	4.81	5.44	8.80	14.08	25.50	43.10	1.2†	49	Started day after hemorrhoidectomy
33	3.76	5.05	10.90	15.18	36.20	46.90	3.0†	49	Ferric ammonium citrate during final 14 days
19	4.56	4.99	10.90	11.45	35.90	36.50	3.0†	49	Inadequate diet before and during treatment

* Ferric ammonium citrate given in solution.
† Ferric ammonium citrate given in capsule form as prepared by Lederle Laboratories.

citrate daily and intramuscular injections of solution liver extract was started. Three injections were given at four day intervals, each dose being 3 cc. derived from 100 Gm. of liver. On May 5, the patient was up and about; she had no cough and stated that she felt very well. The hemoglobin was 50 per cent (Tallqvist); red blood cell count, 2,946,000, and white blood cell count, 5,200. Three more injections were given at weekly intervals, and the iron was continued. On May 29, the hemoglobin was 65 per cent (Tallqvist); red blood cell count, 5,584,000, and white blood cell count, 8,200. No further injections were given, and on June 18, the hemoglobin was 80 per cent (Tallqvist); and the red blood cell count, 5,200,000. The patient was doing her usual work and stated that she had not felt so well for ten years.

Data concerning several other patients similarly treated, which is not being shown in the tables, may be discussed briefly.

The first one, a young woman treated by another Boston physician,[19] had noticed weakness and pallor, and tired easily. When seen in November, 1931, the hemo-

18. Data supplied by Dr. W. W. Barker of Dorchester, Mass.
19. Data supplied by Dr. Lyman Hoyt of Boston.

globin was 70 per cent (Tallqvist), and the red blood cell count, 3,900,000. The red blood cells showed marked variation in size and shape, with achromia. For five months the patient received over 2 Gm. of pills of ferrous carbonate daily, and on April 6, 1932, the hemoglobin was unchanged; the red blood cell count, 3,000,000, and the appearance of the cells, essentially as noted previously. She was

Chart 2.

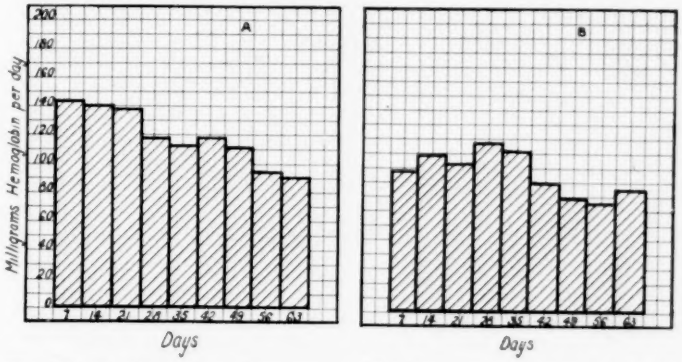


Chart 2.—In *A* are given the averages of fourteen patients treated with pills of ferrous carbonate, U. S. P. (table 5 *A*); in *B*, the averages for sixteen patients treated with ferric ammonium citrate (table 2 *A*).

Chart 3.

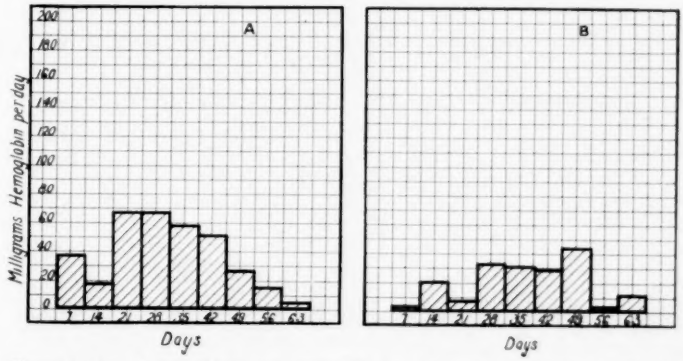


Chart 3.—In *A* are given the averages for six patients treated with ferric citrate (table 4 *A*); in *B*, the averages for three patients treated with liver extract for secondary anemia (Whipple) (table 3 *A*).

then given an injection intramuscularly of 3 cc. of solution of liver extract prepared from 100 Gm. of liver, on each of three successive days. The pills of ferrous carbonate were continued. On April 14, the hemoglobin was 80 per cent (Tallqvist); and the red blood cell count, 4,536,000; the cells were essentially normal in appearance, and the patient stated that she felt very much better.

Another patient entered the hospital in a state of extreme weakness, with a hemoglobin level of 3.31 Gm., and 2,610,000 red blood cells. There was a large palpable mass in the right lower quadrant and loss of blood from the bowel; roentgen evidence of involvement of the intestine by tumor was interpreted as a carcinoma. The patient received ferric ammonium citrate, 3 Gm. daily, and an injection of solution of liver extract intramuscularly at weekly intervals, until her blood was examined again five weeks later, at which time the hemoglobin was 5.80 Gm. and the red blood cell count 3,760,000. Her strength had increased proportionately with the change in her blood.

A fourth patient had been observed elsewhere for a period of ten years because of anemia and hypothyroidism. During the ten year period she took, intermittently, liver extract by mouth, ventriculin, iron, and at times thyroid substance. During this time the red blood cell count rose above 4,000,000 cells per cubic millimeter on only a few occasions, generally varying between 3,500,000 and 4,000,000. On admission to the hospital, the patient presented the picture of

TABLE 4*A*.—*Detailed Record of Changes in the Hemo*

	Initial			Increase in He													
Case	Red Blood Cells	Hemoglobin	Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day	49 Days	
29	3.92	6.76	23.81	....	....	0.34	24.2	....	....	1.93	68.9	2.21	63.1	....	....	4.97	
30	4.81	10.63	32.89	0.14	—20.0	0.28	—20.0	....	....	1.10	39.2	0.96	27.4	1.38	32.8	2.62	
31	4.64	7.87	27.60	....	....	....	....	0.69	32.8	0.82	29.3	1.65	47.2	1.24	29.5	1.59	
32	4.81	8.80	25.50	0.38	—54.3	0.86	61.3	0.11	—5.2	2.58	92.2	....	....	4.50	107.2	5.58	
33	3.76	10.90	36.20	0.55	78.7	0.55	39.3	2.21	105.2	2.21	79.0	3.18†	90.9	4.00	95.4	4.28	
19	4.56	10.90	35.90	....	....	—0.41	—29.2	—0.69	—32.8	—0.27	—9.9	....	....	....	....	0.55	
Average.....				0.01	1.40	0.21	15.0	0.52	25.0	1.39	49.6	2.00	57.1	2.78	66.2	3.25	

* The gain in hemoglobin at intervals of seven days is shown in grams; the gain per day, in milligrams.
† The dose was changed to the same amount of ferric ammonium citrate.

obesity, thick features, constipation and anemia. The hemoglobin was 12.28 Gm.; the red blood cell count, 4,300,000 per cubic millimeter of blood; the basal metabolic rate, minus 23 per cent, and the weight 98.2 Kg. With injections of solution of liver extract, 3 cc. prepared from 100 Gm. of liver at four and five day intervals, ferric ammonium citrate, 3 Gm. daily, doses of thyroid substance varying from 0.015 to 0.045 mg. daily, and a diet containing 1,200 calories, the blood rose within twelve days to a hemoglobin level of 14.49 Gm. and a red blood cell count of 4,700,000, where it remained until discharge at the end of thirty days, at which time the basal metabolic rate was minus 16 per cent and the weight 94 Kg., and the bowels were acting essentially normally.

The last patient to be discussed was first seen at the Boston Lying-In Hospital during her eighth month of pregnancy with a severe degree of anemia. The hemoglobin level at that time was 6.35 Gm.; the red blood cell count, 3,690,000 per cubic millimeter, and the whole blood iron, 18.12 mg. per hundred cubic centimeters of blood. Ferric ammonium citrate crystals had been given for about a week with slight change in the blood level. The patient was then given injections of 3 cc. of solution of liver extract prepared from 100 Gm. of liver at four or five day intervals, and daily by mouth 3 Gm. of ferric ammonium citrate in capsules. Her blood level rose in twenty-four days to 10.9 Gm. of hemoglobin and 4,420,000 red blood cells; the blood iron rose to 39.5 mg., and by thirty days post partum,

to 13.52 Gm. of hemoglobin, 5,090,000 red blood cells and 44 mg. of whole blood iron. Her general condition improved steadily up to the time of discharge from the hospital.

The five cases reported are examples of the types of problems in anemia commonly encountered by the physician in which most pleasing results may be expected from the combination treatment suggested.

COMMENT

The effectiveness of iron in the treatment of anemia of the hypochromic type has been known for many years, and even in the time of Blaud [20] the need for large doses was recognized. Such men as Christian,[21] Lichtenstein,[22] Meulengracht,[23] Osler,[24] Minot [25] and others

Hemo... Patients Treated with Ferric Citrate as in Table 4

...rease in He...													Final			Total Gain		
49 Days	...	Per Day	63 Days	Per Day	70 Days	Per Day	77 Days	Per Day	84 Days	Per Day	91 Days	Per Day	Red Blood Cells	Hemoglobin	Blood Iron	Red Blood Cells	Hemoglobin	Blood Iron
4.97	...	....	....	....	....	....	....	....	....	....	....	....	4.92	11.73	39.60	1.00	4.97	15.8
2.62	...	19.6	....	....	....	....	....	....	....	....	....	....	4.80	11.73	37.31	—0.01	1.10	4.4
1.76	...	12.3	2.48†	35.4	2.89	38.8	3.03	36.1	3.72	40.9	3.72	38.0	5.36	11.59	35.20	0.72	3.72	7.6
5.8	...	....	....	....	....	....	....	....	....	....	....	....	5.44	14.08	43.10	0.63	5.28	17.6
4.8	...	....	....	....	....	....	....	....	....	....	....	....	5.05	15.18	46.90	1.29	4.28	10.7
0.3	...	....	....	....	....	....	....	....	....	....	....	....	4.99	11.45	36.50	0.43	0.55	0.6
3.27	...	15.8	....	....	....	....	....	....	....	....	....	....	....	.....	.....	....	3.32	9.45

noted the improvement which will follow the administration of adequately large doses of iron in a simple form. There is lacking in the literature, however, data obtained as the result of controlled observations on the treatment of secondary anemia in man, which would indicate the relative value of the more common iron salts, of substances other than iron or various means of administering these. Reports as to

20. Blaud, P.: Sur les maladies chlorotiques, et sur un mode de traitement spécifique dans ces affections, Rev. méd. franç. et étrang. **1**:337, 1832.

21. Christian, H. A.: A Sketch of the History of the Treatment of Chlorosis with Iron, M. Libr. & Hist. J. **1**:176 (July) 1903.

22. Lichtenstein, A.: Jahrb. f. Kinderh. **38**:387, 1918.

23. Meulengracht, I.: Large Doses of Iron in the Different Kinds of Anemia in a Medical Department, Acta med. Scandinav. **58**:594, 1923.

24. Osler, W.: Modern Medicine, ed. 3, Philadelphia, Lea & Febiger, 1927, vol. 5, p. 66.

25. Minot, G. R.: Treatment of Anemia, in Christian, H. A., and Mackenzie, J.: Oxford Medicine, New York, Oxford University Press, 1928, vol. 2, pt. 2, p. 649.

the value of the various treatments which have been suggested from time to time for the treatment of human anemia have led to much confusion owing to several factors, some of which are as follows:

TABLE 5A.—*Detailed Record of Changes in the Hemoglobin of Patients Treated with F*

Case†	Initial: Red Blood Cells	Initial: Hemoglobin	Initial: Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day	Increase
1	4.08	4.14	19.40	0.97	138.5	3.59	256.6	5.38	256.3	6.07	217.0	6.35	181.5	6.49	154.4	
2	4.46	5.24	18.10	1.52	217.1	3.45	246.5	3.73	177.7	4.14	147.9	....	.....	....	.....	
3	3.89	8.14	28.00	1.24	177.1	1.38	98.5	2.49	118.6	2.49	80.9	2.90	54.2	3.07	73.1	
4	4.09	6.62	21.30	0	0	1.52	108.5	....	.....	2.63	93.8	....	.....	....	.....	
5	2.96	7.59	25.20	2.07	395.8	....	.....	4.00	190.5	....	.....	....	.....	....	.....	
6	2.16	4.14	16.10	....	.....	0.69	49.3	....	.....	....	.....	....	.....	5.80	138.1	
X1	5.24	7.04	29.20	0.55	78.6	1.10	78.5	2.34	111.2	2.21	78.8	2.76	62.3	4.48	106.6	
X2	2.56	4.28	15.75	1.10	157.0	2.62	186.9	....	.....	6.62	236.5	7.31	209.1	8.55	201.1	
13	4.99	6.07	20.20	0.42	60.0	3.04	217.1	4.69	223.5	....	.....	....	.....	6.90	164.4	
14	4.25	6.90	23.60	0.97	138.5	3.31	236.4	2.76	131.4	2.07	71.8	3.31	94.5	3.59	85.5	
15	3.42	6.07	25.90	....	.....	0.55	39.3	2.49	118.6	2.21	78.8	....	.....	3.87	92.2	
16	4.00	8.56	31.40	0.27	38.5	....	.....	2.07	98.5	2.34	83.6	3.06	87.4	....	.....	
17	3.48	6.90	24.20	....	.....	....	.....	1.38	65.7	....	.....	....	.....	....	.....	
18	4.88	7.73	24.90	....	.....	0.69	49.3	1.10	52.3	2.90	103.6	....	.....	2.48	59.1	
Averages.....				1.01	144.6	1.99	142.4	2.94	140.4	3.37	119.4	4.28	114.9	5.02	119.4	

* The gain in hemoglobin at intervals of seven days is shown in grams; the gain per day, in milligrams.
† These case numbers are used in previous papers.[4] The patients in the last six cases also received fraction G of

TABLE 6A.—*Detailed Record of Changes in the Hemoglo*

Case†	Initial: Red Blood Cells	Initial: Hemoglobin	Initial: Blood Iron	7 Days	Per Day	14 Days	Per Day	21 Days	Per Day	28 Days	Per Day	35 Days	Per Day	42 Days	Per Day	Increase
7	2.98	6.76	26.60	2.07	295.8	....	.....	3.45	168.6	3.59	128.2	3.45	98.5	4.14	98.5	
8	3.05	4.55	17.60	....	.....	....	.....	....	.....	4.01	143.1	2.90	82.9	3.73	106.6	
9	3.85	3.45	16.90	3.45	493.0	4.83	344.9	6.21	296.1	6.21	222.1	6.90	197.0	....	.....	
10	3.98	5.52	19.00	0.69	98.5	1.38	98.5	3.17	150.9	3.17	113.3	3.45	98.5	....	.....	
11	2.96	7.73	26.30	0.96	137.2	3.59	256.6	4.00	190.5	4.00	143.0	4.55	130.0	....	.....	
12	3.56	9.80	28.50	0.27	38.5	0.69	49.3	1.65	78.5	1.93	68.9	2.07	59.1	2.62	74.8	
30667	2.20	4.55	.....	....	.....	1.80	128.6	2.63	125.2	4.83	172.6	5.39	154.0	7.04	167.6	
Averages.....				1.48	212.6	2.45	175.6	3.52	168.3	3.96	141.6	4.10	117.1	4.38	111.7	

* The gain in hemoglobin at intervals of seven days is shown in grams; the gain per day, in milligrams.
† These case numbers were used in previous papers.[4]
‡ The results are obtained by the Kennedy method and are not comparable with others.

1. The control observations are inadequate in order to establish a knowledge of the results which may be expected under uniform circumstances. Cases of anemia of similar origin must be used and data recording the effect thereon of a uniform and simple iron preparation should be available for comparison.

2. The periods of observation are of too short duration to get the maximum effect. The figures in the tables suggest that in the majority of instances the maximum effect of treatment occurs between the second

Carbonate (1.8 Gm.) Alone or Together with Liver Extract (Cohn Fraction G)

											Final			Total Gain		
	56 Days	Per Day	63 Days	Per Day	70 Days	Per Day	77 Days	Per Day	84 Days	Per Day	Red Blood Cells	Hemoglobin	Blood Iron	Red Blood Cells	Hemoglobin	Blood Iron
	....	.....	....	.....	7.45	106.5	....	.....	....	.....	5.31	11.59	41.80	1.23	7.45	22.40
	6.21	111.1	....	.....	6.90	98.6	....	.....	7.73	92.1	5.14	12.97	37.50	0.68	7.73	19.40
	....	.....	....	.....	....	.....	....	.....	3.87	46.1	4.56	12.01	41.40	0.67	3.87	13.40
	4.81	86.3	....	.....	....	.....	....	.....	....	.....	5.00	11.45	39.00	0.91	4.83	17.70
	....	.....	....	.....	....	.....	....	.....	....	.....	4.64	11.59	44.00	1.68	4.00	18.80
	7.31	130.8	....	.....	....	.....	....	.....	....	.....	4.09	11.45	37.90	1.93	7.31	20.90
	4.14	73.9	4.55	72.3	4.14	59.1	4.97	64.4	4.55	53.6	5.49	11.59	38.15	0.25	4.55	8.95
	....	.....	10.07	160.0	....	.....	....	.....	....	.....	4.44	14.35	43.80	1.88	10.07	28.05
	....	.....	....	.....	....	.....	5.94	77.0	....	.....	5.50	12.01	41.60	0.51	5.94	21.40
	....	.....	....	.....	....	.....	3.31	43.0	....	.....	4.50	10.21	44.40	0.25	3.31	29.80
	....	.....	....	.....	....	.....	5.11	66.5	....	.....	5.34	11.18	39.50	1.92	5.11	14.00
	....	.....	3.17	50.3	....	.....	....	.....	....	.....	4.97	11.73	39.30	0.97	3.17	7.50
	4.42	78.8	....	.....	....	.....	....	.....	....	.....	4.98	11.32	35.10	1.50	4.42	10.80
	....	.....	....	.....	....	.....	....	.....	....	.....	4.73	11.04	41.90	−0.15	3.31	17.00
	5.38	96.1	5.93	94.3	6.16	88.0	4.83	62.7	5.38	63.9	....	.....	.....	....	5.36	17.25

s Treated with Ferrous Carbonate (1.8 Gm.), and Whole Liver

											Final			Total Gain		
	56 Days	Per Day	63 Days	Per Day	70 Days	Per Day	77 Days	Per Day	84 Days	Per Day	Red Blood Cells	Hemoglobin	Blood Iron	Red Blood Cells	Hemoglobin	Blood Iron
	3.59	64.1	....	.....	....	.....	....	.....	4.42	5.36	4.99	11.18	37.3	2.01	4.42	10.7
	6.49	115.7	6.77	106.2	....	.....	7.32	95.1	8.70	102.6	4.85	13.25	41.10	1.80	8.70	23.50
	....	.....	....	.....	....	.....	....	.....	....	.....	5.23	11.04	36.70	1.38	7.59	19.80
	....	.....	....	.....	....	.....	....	.....	....	.....	5.30	11.73	38.00	1.32	6.21	19.00
	5.24	93.4	4.41	70.1	....	.....	....	.....	....	.....	5.01	12.14	38.60	2.05	4.41	12.30
	....	.....	....	.....	3.03	43.3	....	.....	....	.....	4.74	12.83	41.40	1.18	3.03	12.90
	....	.....	....	.....	....	.....	....	.....	....	.....	4.10	11.45	.....	1.90	6.90	.....
	5.11	91.1	5.59	88.1	3.03	43.3	7.32	95.1	6.56	78.1	....	.....	.....	....	5.89	16.36

and fourth weeks after the beginning of treatment. It is therefore apparent that a change of therapy made during this interval would lead to results which may be misinterpreted. The second form of treatment would then receive credit for results actually produced by the first form of treatment.

3. The effect of any form of treatment on a specific type of anemia in animals cannot be interpreted as indicating its value in the anemias of man, the origin of which may be entirely different.

In carrying on the study which is reported in this and two preceding papers,[4] an effort has been made to utilize patients for treatment who have anemia of the hypochromic type, either idiopathic, combined with dietary inadequacies, or produced by chronic loss of blood. In a few instances, alveolar abscesses or pyorrhea have been present, but they were usually treated during the course of medication. Occasionally other complications such as arthritis or gallbladder disease have been present. In these and similar instances, one may probably expect less rapid improvement than in a similarly treated patient without complication.

TABLE 7.—*Clinical Results*

	Total Average Gain in Hemoglobin, Gm.	Total Average Gain in Whole Blood Iron, Mg.	Hemoglobin Calculated from Whole Blood Iron, Gm.	Average Daily Gain Over Whole Period, Mg.
Secondary fraction	1.33	3.84	1.17	2.28
Intravenous iron	1.79	4.59	1.40	34.2
Ferric citrate	3.32	9.45	2.88	58.0
Ferric ammonium citrate	5.64	17.48	4.61	73.7
Ferrous carbonate	5.36	17.25	5.26	82.4
Ferrous carbonate and whole liver	5.89	16.36*	5.36*	92.1
Solution liver extract intramuscularly and ferric ammonium citrate	6.47†	19.57	5.97	153.2†

* These results were obtained by the Kennedy method and are not comparable with others.
† This figure is based on results observed in nineteen patients, seven of whom were treated after the paper was presented for publication, and data showing the rate of improvement are not recorded in tables 1 and 1A.

It has been the policy to advise the patient to take an adequate well balanced diet, essentially as advised by Minot and Murphy.[14] A few of the patients were unable to take an entirely adequate diet owing to their financial status, and in these patients improvement has been less satisfactory than in those able to take the regulation diet. Although a few of the patients were started on treatment during a period of observation in the hospital, they have all been ambulatory during the greater part of the period of treatment.

From a comparison of the observations recorded in earlier papers with those of this paper, it appears that the most striking improvement occurred in those patients who received intramuscular injections of solution of liver extract (Lederle) together with iron by mouth and in those who ingested rather large amounts (240 Gm.) of whole liver[1] daily together with iron. This suggests that the iron ingested is utilized more efficiently when given in conjunction with a substance which will build the "stroma" (Whipple[26]) of the red blood cells. That such a condition actually occurs is very well shown in those patients who

26. Whipple, G. H.: Pigment Metabolism and Regeneration of Hemoglobin in the Body, Arch. Int. Med. **29**:711 (June) 1922.

received the intramuscular injections of solution of liver extract alone for a period of time and then with iron by mouth. In some cases the red blood cell count was seen to increase following the injections, but only after the addition of iron therapy did the hemoglobin level rise, and then rapidly. That whole liver will increase particularly the stroma of the red blood cells in anemia other than pernicious is suggested by the data recorded in a previous paper.[1] Reznikoff [27] has shown also that iron is retained in a normal subject to a greater degree when injections of a liver solution are given intramuscularly than without its use.

This need on the part of the blood-forming organs to have stroma-building material available in order that the iron may be utilized to the best advantage is comparable to the situation which occurs during the treatment of pernicious anemia by means of intramuscular injections of a solution of liver extract, except that in the latter case the iron supply becomes inadequate during the rapid production of red blood cells and improvement will be greater if iron is supplied during the course of treatment. Owing to the high iron content of whole liver and the green vegetables, such a situation does not often arise when a patient with pernicious anemia is treated with whole liver and the anemia diet.

In those patients in whom the principal form of therapy was a simple iron salt there appears to be some difference between the effectiveness of the three salts used. The patients receiving pills of ferrous carbonate or ferric ammonium citrate showed better responses than did those receiving ferric citrate. Although the smaller or minimal doses of iron were sufficient in practically every instance to cause reasonably satisfactory improvement, there is likely to be a lag in the formation of hemoglobin as the normal level is approached. In those patients who received the larger doses of iron, improvement was somewhat more rapid and more nearly normal levels were reached than in those receiving less iron, but the rate of improvement was not directly proportional to the amount of iron given.

Although ferric ammonium citrate and ferrous carbonate have been effective when given in amounts sufficient to supply approximately from 170 to 180 mg. of iron daily, such a dose is probably a minimally effective one and not sufficient to produce as satisfactory improvement in the blood of the majority of patients as may be possible with larger doses. On the other hand, doses of the iron salts supplying approximately 1,000 mg. of iron daily have not been more effective than doses supplying 500 mg. of iron. The optimal and most economical dose of these iron salts for the majority of patients is therefore that amount which will supply daily 500 mg. of iron.

27. Reznikoff, P.: Iron Metabolism Studies, Proc. A. Soc. Clin. Investigation **11**:807 (July) 1932.

An important feature of the studies carried out has been the lack of evidence to suggest that special combinations of iron with other substances for administration by mouth have any definite value over the use of the simple iron salts in the treatment of the types of anemia treated. The special preparations containing iron are apparently utilized less effectively than the simple iron salts, often more disagreeable to the patient, and invariably more expensive.

Although the number of patients treated in each separate group may be considered insufficient to establish beyond doubt the actual value of each type of therapy employed, there can remain little doubt but that large amounts of iron should be used in preference to the minimal dose in order to obtain optimal results in a larger percentage of patients, and that improvement of both patient and blood will take place more rapidly and to a more satisfactory degree when iron therapy is combined with intramuscular injections of a solution of liver extract or perhaps with whole liver by mouth. Large amounts of liver, however, are taken less readily by patients with this type of anemia than by those with pernicious anemia.

It is hoped that the results recorded in the three papers may be of value as a control group for those who may carry on the treatment of anemia with other substances.

SUMMARY

The results of treatment by various means of a group of patients with anemia of the hypochromic type are recorded.

A comparison of the effect on the blood of the types of treatment carried out and reported in this and two previous papers is made and the following conclusions drawn:

1. Treatment by means of intramuscular injections of solution of liver extract (Lederle) together with adequate doses of iron (ferric ammonium citrate) by mouth is the most effective, although the combination of large doses of whole liver and iron by mouth is very effective but less readily used.

2. Of the various substances other than whole liver which were given by mouth, ferric ammonium citrate and pills of ferrous carbonate U. S. P. were about equally effective and outranked the others in blood-building effect. The optimal dose of these salts is that which supplies daily 500 mg. of iron (ferric ammonium citrate, 3 Gm.; pills of ferrous carbonate, 5.4 Gm.).

3. Iron hydroxide used intravenously proved to be moderately effective but without advantage over the iron administered by mouth.

Isabel Howard gave expert technical assistance.

311 Beacon Street.

AVITAMINOSIS IN NATIVES OF RHODESIA

TREATMENT OF EPIDEMIC SCURVY BY THE INTRAVENOUS INJECTION OF CITRUS

T. J. DRY, M.A., M.B., CH.B.
Fellow in Medicine, the Mayo Foundation
ROCHESTER, MINN.

Since the cause of most deficiency diseases has been established, and since an efficacious and easily available cure has been found to exist in the observance of what is now regarded as a protective and well balanced diet, there is a strong tendency to regard these diseases as belonging to the bygone prescientific ages. This, together with the fact that ill health may be produced by deficiency of a food factor in amounts much smaller than those necessary to create the typical full-blown picture associated with its lack, explains why the deficiency syndromes are more common than their diagnosis. It is to be expected, therefore, that deficiency syndromes may occur in persons existing for any considerable length of time on a restricted diet, either therapeutic or voluntary, or as a result of dietary eccentricities.

Davidson [1] reported three cases of deficiency disease in patients on a diet prescribed for ulcer. He called attention to the fact that in the overwhelming enthusiasm for controlling obvious functional derangements by dietetic measures, the maintenance of the patient on a diet containing the necessary accessory food factors is often ignored.

A diet prescribed for colitis,[2] consisting of rice, milk, eggs, white meats and broth, led to the development of scurvy after eleven months. Mettier, Minot and Townsend [3] reported nine cases of avitaminosis following restriction of food. Martin [4] reported a severe scorbutic condition in a patient who had been under dietetic and alkaline treatment for duodenal ulcer for six months; the condition was precipitated by an attack of influenza, thus illustrating, as many others have shown, the importance

---

Work done while a medical officer of the Rhodesian Railways, 1931.

1. Davidson, P. B.: The Development of Deficiency Disease During Therapeutic Diets, J. A. M. A. **90**:1014 (March 31) 1928.

2. Immerman, S. L.: Scurvy Following a Restricted Diet in Colitis, J. A. M. A. **94**:1757 (May 31) 1930.

3. Mettier, S. R.; Minot, G. R., and Townsend, W. C.: Scurvy in Adults; Especially Effect of Food Rich in Vitamin C on Blood Formation, J. A. M. A. **95**:1089 (Oct. 11) 1930.

4. Martin, H. E.: Scurvy Following an Ulcer Diet, Lancet **2**:293 (Aug. 8) 1931.

of auxiliary factors in the causation of deficiency syndromes. Bullowa,[5] Giorgi,[6] and Swanson[7] are among contributors to the literature who show the importance of being on the outlook for such diseases if the diet in any way diverges from the normal, or if nutritional disturbances arise from coexisting disease. Swanson reported the only case I was able to find in the literature in which scurvy developed as a result of continued vomiting during pregnancy. Hyperemesis, commencing two months prior to the onset of purpuric phenomena, had been preceded by a diet high in vitamins. The onset of scorbutic features was sufficiently dramatic to suggest the presence of one of the blood dyscrasias, but examination of the blood and the subsequent course of events showed it to be a case of scurvy. The disturbance of the mineral metabolism under these circumstances may have been a factor in the severity of the purpura.

Cases in which deficiency disease assumes epidemic proportions are of particular interest since they illustrate more effectively the variety and the number of contributing causes, as well as the ease with which such outbreaks may be controlled with institution of proper treatment. Both of these principles as well as many aspects of faulty nutrition are well demonstrated by an outbreak of scurvy among the native laborers in the railroad reconstruction camps in Southern Rhodesia during 1931. A description of the prevailing conditions and of the mode of living of the native (Kaffir) follows:

The natives concerned, of which there were about 10,000, were drawn principally from the Northern Rhodesian territories, in some instances several hundred miles from the area under consideration, and were employed as laborers on railroad reconstruction from Victoria Falls to a point 75 miles south. They were distributed in a series of camps along this stretch, which served as their temporary homes while under contract.

In his native surroundings the Kaffir leads an undisturbed existence. By disposition he is leisurely, unselfishly allowing his women folk and pickaninnies to indulge in tilling the soil or herding the few cattle or small flock of sheep and in preparing the national beverage of "kaffir beer." "The noble male must hunt; the woman may dig in the dirt." applies here very well. Hence his food supplies fluctuate with fortune, with the seasons and with his ingenuity in trapping game, and he is

5. Bullowa, J. G. M.: Self-Induced Avitaminosis: Beriberi and Scurvy; Medicolegal Aspects; Period for Development and for Cure, M. Clin. North America **10**:959 (Jan.) 1927.

6. Giorgi, E.: Epidemic Scurvy, Pediatria **29**:66 (Jan. 15) 1921; abstr., J. A. M. A. **76**:689 (March 5) 1921.

7. Swanson, C. N.: Scurvy Complicating Vomiting of Pregnancy, J. A. M. A. **88**:26 (Jan. 1) 1927.

often saved by the grace of good government from dying of starvation. But despite periods of deprivation, fully developed deficiency syndromes are rare among the Kaffirs when in their native environment. In lean times they seek food and occupation from the European settlers; at other times recruiting agents gather large numbers of them to seats of mining and construction activities, where the weak and the aged have often to be included in order to capture the services of their more robust brother. This is a very unfortunate but apparently unavoidable state of affairs, and explains largely why the average native under consideration is of rather poor physique.

The distance to the nearest railway center is in many cases considerable, and the Kaffir travels most often on foot, carrying all his personal belongings, with but little food for himself and his wife and family who accompany him. It is conceivable, then, that when he arrives at his destination he is all but starved.

A consideration of the etiology of deficiency diseases in general would include some of the important predisposing factors already mentioned. The natives who had not already manifest signs of scurvy would soon succumb to the effects of what, to them at any rate, is hard physical labor, in totally new surroundings, with the contributing factor of mental depression induced by what probably is their first encounter with the hardships of life.

Should this impart the idea that native laborers are loaded with overburdening tasks, I should like to dispel such impressions by saying that the government appoints labor inspectors for their protection and their interests. But it cannot be too strongly emphasized that in a previously undernourished person the extra metabolism attendant on work hastens the exhaustion of vitamins, so that soon a latent deficiency disease will appear. Even in the days of Captain Cook's [8] expeditions it was known that longer hours of sleep were important in combating the effects of supplies low in vitamins and the onset of the sailors' dreaded disease.

Once the Kaffir is employed, he is fed according to government regulations, which include all the essentials of what has come to be regarded as a protective diet, and which in fact is a very liberal diet. But at the onset he is usually somewhat averse to eating the green vegetables of the white man, and until he has learned their value, he is likely to discard them. The one criticism of the diet is its high carbohydrate content. As McCarrison [9] and others have shown, lack of

8. Angus, T. S.: Captain Cook's Hygiene, Brit. M. J. **2**:1233 (Dec. 31) 1927.

9. McCarrison, Robert: Studies in Deficiency Disease, New York, Oxford University Press, 1921.

balance in diet is almost as important as the restriction of vitamins in the production of deficiency disease.

The important sources of vitamins in the government ration scheme were green vegetables, meat and beans (which are sprouted prior to cooking), but the native was as likely to discard these as he was to render them valueless by excessive cooking. The natives were also allowed to make a certain amount of kaffir beer (or leting), a brew in which sprouted cereal (usually kaffir corn or "sorghum vulgare") is used as malt. It is of low alcoholic content and contains a small amount of vitamin C. In a study of scurvy, as it occurs on the Rand Gold Mines in South Africa, Delf [10] emphasized its value in the diet of the native. The same investigator has shown that about 200 cc. of the brew was effective in protecting monkeys from developing scurvy. At least it can be said that the right of brewing his beer makes the native a happier individual, and its consumption at least induces a state of artificial euphoria in one neither highly pleased with life nor overcheerful in surroundings which are so totally unlike those of his natural environment.

Besides the specific deficiency in vitamins and the accessory factors, such as previous undernourishment, muscular exertion and mental depression already mentioned, any condition which lowers the general resistance, increases the metabolic burden or adds to nutritional defects will hasten the onset of manifest scurvy or add to the seriousness of the clinical picture.

Hardly a native escapes infection with intestinal parasites, especially ankylostomiasis. Darling [11] asserted that 75 per cent of microscopic examinations of stools revealed infection, and treatment with vermifuge leads to recovery of worms or their ova in about 98 per cent of cases. Dysentery, both amebic and bacillary, and indeterminate forms of diarrhea are common enough to duplicate the already high morbidity accounted for by recurrent attacks of malaria. The relation between avitaminosis and infections has been widely considered in the literature. McCarrison,[12] among others, has provided much evidence of lowered resistance to infection as a result of deprivation of vitamins. More especially is the integrity of the covering epithelial structures affected, allowing infection to occur more readily, so that a specific anti-infective factor has found its place in the classification of vitamins.

10. Delf, E. M.: Studies in Experimental Scurvy, with Special Reference to the Antiscorbutic Properties of Some South African Foodstuffs, Lancet **1**:576 (March 25) 1922.

11. Darling, quoted by Manson-Bahr, P. H.: Scurvy in the Tropics in Manson: Tropical Disease, ed. 8, New York, William Woods & Company, 1925, p. 337.

12. McCarrison, Robert: Some Surgical Aspects of Faulty Nutrition, Brit. M. J. **1**:966 (June 6) 1931.

It is equally true that scurvy is often precipitated by infective febrile illnesses, probably due to the fact that the increased metabolism associated with fever exhausts more rapidly the supply of vitamin, much in the same way as exercise does. In this respect, then, it is analogous to the facts known about the decreased action of insulin under similar circumstances; but scurvy in itself appears to cause an elevation of the metabolic rate. This observation was made by Knipping and Kowitz [13] who found that a previously increased basal metabolic rate in cases of avitaminosis was reduced to normal by the addition of orange juice to the diet.

Lind [14] reported an outbreak of scurvy among the inmates of an asylum in Victoria (Australia) which illustrates the part infection plays in the causation of scurvy. In this instance there had been no alteration in the diet of the patients for years, but an infectious condition (the nature of which was not determined) caused a febrile illness and led to an outbreak of the disease in epidemic form.

Race, age and sex enter into the consideration of the etiology of scurvy. One subtribe of the great Barotsi race, known as the Mulhivali, contributed about 80 per cent of the total number of scorbutic patients at the construction camps. This race presents several interesting features. First, they are regarded as the most savage of Northern Rhodesian tribes. Second, as a tribal custom their teeth are filed into sharp, peg-shaped structures. The dental decay following this procedure would certainly account for the marked scorbutic features of their gums, even if the disease is mild.

Women and children were noticeably free from scurvy; probably for once the general order of life was reversed, and it was they who led the leisurely life while the father of the family was earning the daily bread. A final factor worthy of mention was the fact that native employers had depended on the use of crude lime juice as a prophylactic agent against deficiency disease, an extract which has been proved experimentally by Chick, Hume, Skelton and Smith [15] to be almost entirely devoid of antiscorbutic properties. The same writers record some interesting facts relative to the arctic expeditions of the nineteenth century. Thus the crew of "The Investigator," 1850, enjoyed remarkable immunity from scurvy for the first and second years, whereas those of a subsequent expedition on "The Alert and The Discovery" 1875,

13. Knipping, H. W., and Kowitz: Untersuchungen über die Avitaminose beim Menschen, München. med. Wchnschr. **1**:46 (Jan. 12) 1923.

14. Lind, W. A. T.: Some Interesting Details of an Outbreak of Scorbutus, M. J. Australia **2**:107 (Aug. 9) 1919.

15. Chick, Harriette; Hume, E. Margaret; Skelton, Ruth F., and Smith, Alice H.: (A) Experimental Inquiry: The Relative Content of Antiscorbutic Principle in Limes and Lemons; (B) Historical Inquiry, Lancet **2**:735 (Nov. 30) 1918.

suffered severely at the end of the first winter spent in the arctic regions, for although the former used lemon juice, the latter were supplied with limes.

The pathologic changes are essentially the occurrence of hemorrhages of varying degrees into various parts of the body, the nature of which is not entirely clear. From the hematologic standpoint, anemia with a corresponding reduction in hemoglobin is the only constant symptom, with relative absence of the usual evidences of secondary anemia, suggesting a condition of relative aplasia of the bone marrow. Piney [16] corroborated this observation. Platelets do not appear to be reduced. From a study of thirteen cases of scurvy Shattuck [17] claimed that the platelet counts, bleeding time, coagulation and clot retractility are normal. Bedson [18] studied the platelets both in man and in monkeys and guinea-pigs, and suggested that hemorrhages occur during transient reduction of the platelets, although the figures quoted as obtained by him on repeated examinations both before and after scorbutic symptoms are present do not justify his assumption, since they all fall well within the normal range. Mettier, Minot and Townsend have studied the bone marrow obtained by biopsy from the sternum and claim that it resembles the picture seen in secondary anemia. After treatment such studies indicate marked reactivity of the marrow which then contains numerous mitotic figures and increased numbers of nucleated erythrocytes. It appears then that anemia is due not only to undernutrition, loss of blood and intercurrent infections, but also to inadequate function of the bone marrow dependent on a chronic lack of vitamin C. On instituting treatment, a reticulocyte response is noted which commences on the third day, reaches its peak about the eighth day and then declines. Figures as high as 9.9 per cent reticulocytes were recorded under these circumstances. The leukocytes in uncomplicated scurvy are normal.

Experiments have been carried out indicating absence of metabolic disturbances except such changes as can be accounted for by inanition attendant on the end-stages of advanced scurvy. Humphreys and Zilva [19] reported that there is no deviation from the normal in the absorption or retention of calcium and phosphorus before or during the development of scurvy in guinea-pigs until the last stages of the

16. Piney, Alfred: Recent Advances in Hematology, ed. 2, London, J. & A. Churchill, 1928.

17. Shattuck, G. C.: Scurvy with Reference Especially to Adults, J. A. M. A. **90**:1861 (June 9) 1928.

18. Bedson, S. P.: The Blood Picture in Scurvy, with Particular Reference to the Platelet, Brit. M. J. **2**:792 (Nov. 12) 1921.

19. Humphreys, F. E., and Zilva, S. S.: Metabolism in Scurvy: III. The Absorption and Retention of Calcium and Phosphorus by Guinea-Pigs, Biochem. J. **25**:579, 1931.

experiment, when all physiologic functions of the animal become deranged by the disease. The experiments of Howard and Ingvaldsen [20] carried out to determine whether an explanation of the pathogenesis of scurvy could be found in aberrations of the mineral metabolism, failed to reveal evidence sufficiently significant to draw such conclusions. That there should be rapid nitrogen loss in scurvy is to be expected, and this was found to be the case by the last named investigators as well as by Caridroit,[21] and by Nagayama and Sato.[22] Blood sugar levels,[23] glycogen content [24] of the liver and the carbohydrate metabolism as a whole are normal, whereas lipoid metabolism [25] is only disturbed in the final stages of the experiment.

SYMPTOMS

The main features of fully developed scurvy in the native need be mentioned only briefly here. The facies is characteristic. His complexion is muddy, as if he were unwashed. In an epidemic, a native who walks with a limp is to be strongly suspected of being scorbutic. Careful examination proved this to be the case in many instances. The gums show the characteristic sponginess and bleed easily. However, it should be remembered that when the teeth are in good condition the changes in the gums may be in abeyance until the late stages of the disease. The relation between avitaminosis and dental caries has been commented on in the current literature. Suffice it to mention here that carious teeth were extremely common among natives afflicted with the disease, and this is of unusual interest as the African aborigines are credited with as nearly perfect teeth as are possible to be found.

Hemorrhages in various parts form the prominent feature of the scorbutic subject. The petechiae around the hair follicles on the legs,

20. Howard, C. P., and Ingvaldsen, T.: The Mineral Metabolism of Scurvy of the Monkey, Bull. Johns Hopkins Hosp. **28**:222 (July) 1917.

21. Caridroit, F.: Variation de l'excrétion azotée (azote total urinaire) au cours du scorbut expérimental, Compt. rend. Soc. de biol. **90**:1379 (May 24) 1924; abstr., J. A. M. A. **83**:226 (July 19) 1924.

22. Nagayama, T., and Sato, N.: Studies in Experimental Scurvy: Nitrogen Metabolism of the Animal Fed on Vitamin C Free Diet, J. Biochem. **10**:27 (Oct.) 1928.

23. Nagayama, T.; Machida, H., and Takeda, Y.: Studies in Experimental Scurvy: Carbohydrate Metabolism of Animal Fed on Vitamin C Free Diet, J. Biochem. **10**:17 (Oct.) 1928.

24. Koga, Y.: Studies in Experimental Scurvy; Contribution to Study on Carbohydrate Metabolism of Guinea Pigs Fed on Vitamin C Free Diet, J. Biochem. **11**:461 (Jan.) 1930.

25. Nagayama, T., and Tagaya, T.: Studies in Experimental Scurvy: Lipoid Metabolism of Guinea Pigs Fed on Vitamin C Free Diet, J. Biochem. **11**:225 (Oct.) 1929.

of the earlier stages, naturally cannot easily be detected in the black skin. Extensive bleeding into the subcutaneous, subperiosteal and intermuscular spaces leads to the severe crippling and painful condition associated with the disease, whereas the larger weight-bearing joints and mucous membranes may be similarly affected. I recall one case which, in addition to the usual evidences of scurvy, presented all the classic signs of a mediastinal tumor. Treatment of the scorbutic condition led to dramatic relief of symptoms and the disappearance of all the signs which had led one to suspect a tumor of a more serious nature. Similarly, scorbutic hemorrhages may lead to confusing symptoms and erroneous diagnoses, especially when the usual signs of scurvy are not prominent or not looked for. Sammis [26] reported a case of scurvy in which a subdural hemorrhage was the cause of death. The spinal cord may be similarly involved, whereas abdominal emergency conditions may be diagnosed when hemorrhage occurs into the bowel. Such a case is described by Foote.[27] A child, aged 2½ years, had symptoms of abdominal spasms and passed blood-streaked stools; the gums were normal and although the clinical picture closely simulated intussusception, exploration was delayed until purpuric spots developed, when a diagnosis of scurvy was made. Complete and rapid recovery followed the usual antiscorbutic treatment. The skin overlying hematomas becomes hard and leathery to the touch. The condition of the blood has been mentioned.

Gastro-intestinal symptoms were not frequently complained of, but it is possible that the deficiency of vitamins may have accounted for at least some of the cases of indeterminate diarrhea. Mackie and Chitre [28] found that the colon of the monkey is very sensitive to deficiency of vitamins, especially vitamin C, which causes a condition varying from local congestion and thickening of the mucous membrane to one indistinguishable from ulcerating and sloughing dysentery.

The time required for scorbutic signs to become manifest naturally varies greatly. Dyke [29] reported an outbreak among the men of the South African Native Labor Corps in France during the war, three or four months after their arrival. About 40 per cent of the particular group were affected, and here the predisposing factors must have been somewhat similar to those affecting the natives under consideration. In the latter group, I became associated with the work after the construction

26. Sammis, J. F.: Scurvy with Cerebral Hemorrhage, Arch. Pediat. **36**:274 (May) 1919.

27. Foote, R. R.: Scurvy Simulating Acute Intussusception, Brit. M. J. **1**:1035 (June 19) 1926.

28. Mackie and Chitre, quoted by McCarrison: Brit. M. J. **1**:966 (June 6) 1931.

29. Dyke, H. W.: Outbreak of Scurvy in the South African Native Labour Corps, Lancet **2**:513 (Oct. 19) 1918.

had been in progress for about five months. At that time 80 per cent of persons reported to be ill had scurvy, and the total number of natives affected in varying degrees must have been 60 per cent of those in the camps.

The onset is, as a rule, insidious, with loss of weight, progressive anemia and a feeling of stiffness in the legs. Either at this stage or when definite purpuric manifestations are present, other signs and symptoms may be present which are difficult to dissociate from true scurvy and which are actually included by some writers in the scorbutic syndrome. Many complained of hemeralopia. Bryson [30] claimed that night blindness is: (1) an early or initial symptom of scurvy, (2) the main symptom, the other symptoms being slighter than usual, or (3) a symptom coexisting with fully developed scurvy.

Deficiency edema, mild or advanced, was even more frequently met in sufferers from scurvy. This is of the nature of hunger edema of infants, and it is not always possible to elicit edema until correct diet initiates such extensive diuresis as to transform what seemed like a well-fed child into a veritable skeleton. Walgren [31] has mentioned the invisible edema of scurvy based probably on an increased state of permeability of the capillary walls, but it is more likely that hunger edema is due to a decreased level of plasma protein as in nephrosis and in plasmapheresis. During periods of food deprivation, several factors in the diet may be responsible for deficiency syndromes, and under such conditions it may be impossible to determine which individual components of the clinical picture are due to a particular deficiency. That the plasma proteins may be low in hunger edema has been proved by Liu, Chu, Wang and Chung,[32] who studied the problem in cases of edema of the nutritional type occurring in the inmates of an orphanage. In the cases studied the total plasma protein was as low as 3.46 per cent (the albumin fraction being 1.43 per cent in the same case). Until it can be shown that the edema fluid contains an increased amount of proteins, one cannot depend on an increased capillary permeability for the explanation of a particular variety of edema. Here there is not the same massive loss of the albumin fraction in the urine as in nephrosis, and the only reasonable assumption is that the plasma proteins become depleted as a result of protein deficiency in the diet. The last named workers showed also that the food proteins have a qualitative as well

30. Bryson, Alexander: Night-Blindness, in Connection with Scurvy, Roy. London Ophth. Hosp. Rep. **2**:40, 1859.

31. Walgren, Arvid: Zur Symptomatologie und Pathogenese des Oedema scorbuticum invisible, Ztschr. f. Kinderh. **31**:35, 1922.

32. Liu, S. H.; Chu, H. I.; Wang, S. H., and Chung, H. L.: Nutritional Edema: I. Effect of Level and Quality of Protein Intake on Nitrogen Balance, Plasma Proteins and Edema, Proc. Soc. Exper. Biol. & Med. **29**:250 (Dec.) 1931.

as a quantitative relation to hunger edema. Thus the amount of vegetable protein for each kilogram of body weight required to build up plasma protein and to reduce edema is twice as much as the amount of animal protein necessary to secure the same effects.

An interesting parallelism may be drawn between the hemorrhagic features and edema occurring in scurvy on the one hand and those occurring in the anaphylactoid types of purpura on the other, although the mechanism in the two groups of cases is naturally different.

In potential scorbutic subjects, wounds (which were common about the legs) became chronic sores, and until the scurvy is treated this so-called tropical ulcer refuses to heal. This is an entirely different condition from the well known tropical sore of leishmaniasis. The tropical ulcer commences in an abrasion or wound, and is apparently of nonspecific origin, although numerous organisms and spirochetes have been incriminated. It does not respond to antiprotozoal medications administered either locally or intravenously.

Finally, Hess [33] claimed that latent scurvy may be elicited by the tourniquet test.

The prevalence of vitamin C deficiency naturally raises the possibility of other forms of deficiency disease. The possible relationship to dental caries, infections, night blindness and hunger edema has already been considered. Although conjunctivitis was frequently seen, no direct etiologic relation to such a condition can be claimed to exist. Keratomalacia was never encountered.

The pains complained of in the limbs and in many cases the presence of edema naturally lead one to suspect beriberi, but in rare instances only was there any evidence of true peripheral neuritis. The consumption of beans and whole wheat undoubtedly affords sufficient protection against this malady.

Cases of pellagra are not infrequently reported from prisons; apparently the mental changes attendant on the disease bring the afflicted individual into conflict with the law.

Rickets is rarely encountered in South Africa.

TREATMENT

The treatment of scurvy falls under two headings: specific treatment and treatment of the associated pathologic conditions which do not require special mention here.

The high antiscorbutic value of the citrus fruits and the satisfactory response to their use is well known. Under ordinary conditions a simple dietary adjustment meets all requirements, and heroic procedures are

33. Hess, quoted by Manson-Bahr, P. H.: Scurvy in the Tropics, in Manson: Tropical Disease, ed. 8, New York, William Woods & Company, 1925, p. 337.

unwarranted and superfluous. This, then, was the method adopted at the outset. It is to be remembered, however, that the circumstances with which this account deals were somewhat different from those under which medicine is ordinarily practiced, and for completeness of narrative some of the difficulties encountered and the course resorted to are described.

The demand for fresh fruits and vegetables could be met only by importation from considerable distances, since local production of sufficient quantities was not possible. Even so the supplies were not inadequate. But the most serious obstacle was the unwillingness of the native to make use of such supplies once procured. The savage whose mind is warped by fear and superstition and who is blind to the consequences of depending solely on his traditional fare under circumstances so entirely different from his traditional mode of living cannot be readily induced to comprehend either the nature of his illness or the means to rectify it.

The treatment adopted was that carried out at one of the mine hospitals in that area,[34] which consisted in the intravenous administration of specially prepared and neutralized orange or lemon juice. Donaldson[35] has also recommended this method of treatment. Hess and Unger,[36] in 1918, reported on the use of neutralized orange juice intravenously in experimentally produced scurvy of guinea-pigs, claiming a more rapid response than from animals treated as controls by the usual feeding methods. As evidence of the potency of even small amounts of vitamin C when administered in this way, it should be noted that these investigators reduced the vitamin content of their extract appreciably by boiling prior to injection, and yet the recovery of the scorbutic animal was highly satisfactory. That they were fully aware of the thermolability of the antiscorbutic principle is obvious, since they demonstrated in the same series of experiments that when orange juice was submitted to an autoclave for from ten to fifteen minutes at a temperature of 110 C., most but not all of its vitamin C was destroyed. Since orange juice is an entirely unsuitable medium for growth of organisms, there is no necessity for further sterilization by boiling, provided the usual precautions are observed against contaminations.

It cannot be stated accurately how much, if at all, simple neutralization impairs the antiscorbutic value of citrus juices, but such a step

34. Kerr, J. R.: Personal communication to the author.

35. Donaldson, quoted by Manson-Bahr, P. H.: Scurvy in the Tropics, in Manson: Tropical Disease, ed. 8, New York, William Woods & Company, 1925, p. 337.

36. Hess, A. F., and Unger, L. J.: Experiments on Antiscorbutics: Report of an Antiscorbutic for Intravenous Use, Proc. Soc. Exper. Biol. & Med. **15**:141, 1918.

would seem to be essential in their preparation for intravenous medication. Spencer [37] administered unneutralized orange juice to a patient with scurvy in doses of 10 cc. diluted in 150 cc. of physiologic solution of sodium chloride. Apart from the questionable safety of such a procedure, it is hardly a practical treatment to be used as a routine, should the necessity ever arise to administer vitamin by the intravenous route.

Attempts to place an active preparation of vitamin C on the market have failed for the most part on account of its instability. Givens and McClugage [38] claimed that desiccation of orange juice at a temperature of 55 to 60 C. for forty minutes or more did not destroy sufficient vitamin to render the product useless. Since then many similar claims have been made, yet at present, so far as I have been able to ascertain, there is no satisfactory active principle or preparation of vitamin C suitable for intravenous administration.

Emphasizing again the limited use of an intravenous preparation for clinical purposes, the isolation of vitamin C in a pure and potent form would at least herald the advance of our knowledge of the chemistry of the vitamins. Moreover, within recent years the recognition of states of hypervitaminosis (at least with reference to vitamin D [39]) has been shown to be of as much importance as the recognition of the avitaminoses, and such a preparation as vitamin C would lend itself to a useful application in the field of experimental medicine. Owing to the presence of several other vitamins in the citrus juices, the extract considered here can have only limited practical application. However, that it does contain vitamin C in high concentration and that it can be used without any untoward reactions was shown by the results obtained after several thousand such injections. The method used for the preparation of the extract was as follows: The juices were expressed from fresh oranges or lemons, previously immersed in a 5 per cent phenol lotion to sterilize the skin of the fruits. The extract so obtained was filtered under aseptic conditions and then rendered neutral or slightly alkaline in reaction by the addition of 20 per cent sodium hydroxide. This was always freshly prepared and used the same day. The initial dose was 5 cc.; thereafter, from 10 to 15 cc. twice weekly.

In gaging the efficacy of this method and the rapidity of its action, one cannot record definite time intervals since the degree of severity of

37. Spencer, H. A.: Scurvy: Its Treatment with Raw Orange-Juice Intravenously, South African M. Rec. **24**:386 (Sept. 11) 1926.

38. Givens, M. H., and McClugage, H. B.: The Antiscorbutic Property of Fruits: I. An Experimental Study of Dried Orange Juice, Am. J. Dis. Child. **18**:30 (July) 1919.

39. Harris, L. J.: The Mode of Action of Vitamin D: The "Parathyroid" Theory: Clinical Hypervitaminosis, Lancet **1**:1031 (May 14) 1932.

the disease varies so considerably in different cases. However, in comparing the group of patients treated by means of oral administration at the outset with the group treated by the intravenous method, one can definitely state that the rate of recovery was more rapid as shown by the shorter period of hospitalization when the latter form of administration was adopted. Be it said in its favor that it at least appealed to the savage mind.

SUMMARY AND CONCLUSIONS

The frequency of the occurrence of deficiency syndromes among patients on restricted diets for any reason is considered.

An account is given of the various factors which entered into an outbreak of scurvy among Rhodesian native laborers, and of the manifestations of this disease, as well as of associated forms of avitaminosis.

Under most conditions the oral administration of citrus fruits and fresh vegetables has been found to be highly efficient in correcting the ill effects of deprivation of vitamin C. When circumstances similar to those described arise, the intravenous use of especially prepared orange and lemon juices may be relied on as a safe and efficient method of controlling scurvy. That the vitamin C content of citrus juices is not appreciably impaired by neutralization immediately before its administration is evidenced by the rapid recovery of scorbutic patients after its use.

BRONCHIAL DISINFECTION AND IMMUNIZATION

II. EFFECTS IN RABBITS OF INTRABRONCHIAL INJECTIONS OF VACCINES, BACTERIOPHAGE AND ANTIVIRUS

JOHN A. KOLMER, M.D.
PHILADELPHIA

While bronchial disinfection by intrabronchial lavage with various chemotherapeutic agents would appear to be both possible and safe, as determined by experiments on rabbits, and worthy of clinical trial in the treatment of bronchiectasis and other types of chronic suppurative pneumonitis,[1] the results of additional experiments summarized in this paper indicate that local immunization and disinfection of the bronchi by intrabronchial injections of vaccines, antivirus and bacteriophage may offer even greater therapeutic possibilities and prove worthy of clinical trial in the treatment of bronchiectasis and other types of pulmonary suppuration.

Undoubtedly subcutaneous and intracutaneous injections of properly prepared autogenous vaccines are sometimes of therapeutic value in certain cases of chronic bronchitis, especially those associated with allergic asthma, but vaccine therapy has generally failed to be of any particular value in the treatment of bronchiectasis.

It would appear that intrabronchial injections of vaccines and antivirus may open up a new and promising chapter in the treatment of this and other types of the chronic bronchitides if suitable experiments on rabbits show that the procedure is safe and feasible.

PHAGOCYTOSIS IN RELATION TO BRONCHIAL INFECTION

Phagocytosis is undoubtedly the chief mechanism of defense against bronchial infection and likewise the chief and possibly the sole mechanism of recovery. Therefore, anything that may safely be done to increase phagocytosis of the organisms productive of chronic bronchitis and bronchiectasis, and especially of streptococci and staphylococci, may be expected to have therapeutic value.

From the Research Institute of Cutaneous Medicine and the Laboratories of the Graduate School of Medicine of the University of Pennsylvania.

Aided by a grant from the Faculty Research Committee of the Board of Graduate Education and Research of the University of Pennsylvania.

1. Kolmer, J. A.: Bronchial Disinfection and Immunization: I. Effects in Rabbits of Intrabronchial Injections of Various Chemical Disinfectants, Arch. Int. Med., to be published.

In this connection I refer not only to phagocytosis of organisms by microphages (the polymorphonuclear leukocytes) but likewise, and possibly more importantly, to phagocytosis by macrophages with special reference to clasmatocytes. At least the cells of the macrophage system appear to be more phagocytic in chronic infections.

In this connection the macrophages referred to are principally the monocytes of the circulating blood, the capillary endothelium, the epithelium of the aveoli of the lung and more especially the clasmatocytes, and my interest in the latter is based primarily on the investigations of Gay [2] and his associates on the rôle they have apparently played in resistance to, and recovery from, experimental streptococcic pleuritis of rabbits.

While the exact origin of these clasmatocytes, so named by Ranvier [3] and also designated as histiocytes and tissue macrophages, is unknown, Gay expressed the belief that they are derived from connective tissue, and his work has shown that they are mobile, actively phagocytic and undoubtedly important cells of what he has called the macrophage system.

In a study of smears of a large number of bronchial exudates secured bronchoscopically from cases of chronic bronchitis and bronchiectasis, I have experienced difficulty in recognizing the cells, but with the aid of staining with hematoxylin and eosin as well as with neutral red, as described by Gay and Morrison,[4] these large phagocytic ovoid cells with large eccentric or indented nuclei have been found with considerable regularity. I believe that any procedure resulting in their increase may possess therapeutic value.

VACCINES BY INTRABRONCHIAL ADMINISTRATION

As shown by Gay and Morrison, the intrapleural injection of sterile broth, 1 per cent egg white, 1 per cent peptone solution, acacia broth and other substances into the pleural cavities of rabbits has resulted in a great increase in these clasmatocytes in the exudates and pleural tissues, and after seventy-two hours the changes resulted in greatly increased resistance to intrapleural injections of virulent streptococci. According to these investigators, however, the results were not due as much to what was injected as to the time element, and it has occurred to me that intrabronchial injections of vaccines made of heat-killed broth cultures of streptococci and other organisms may serve equally

2. Gay, F. P.: Tissue Resistance and Immunity, J. A. M. A. **97**:1193 (Oct. 24) 1931.

3. Ranvier, M. L.: Des clasmatocytes, Compt. rend. Acad. d. sc. **110**:165, 1890.

4. Gay, F. P., and Morrison, L. F.: Clasmatocytes and Resistance to Streptococcus Infection, J. Infect. Dis. **33**:338 (Oct.) 1923.

well in producing a local mobilization of these and other phagocytic cells.

Furthermore, it may be that a vaccine administered in this manner may cause increased production of antibodies, with special reference to opsonins, by the local tissues (bronchi and parenchyma of the lungs), since it would appear that some evidence has accumulated to show that antibodies are produced primarily and principally by the tissues directly infected and antigenically stimulated. And since opsonins bear an important and essential relationship to the mechanism of phagocytosis, it has occurred to me that intrabronchial injections of autogenous vaccines prepared with broth may serve the dual purpose of increasing the macrophages of the exudates and tissues with special reference to clasmatocytes and increasing the production of specific opsonins so vitally concerned in both microphagic and macrophagic phagocytosis.

ANTIVIRUS BY INTRABRONCHIAL ADMINISTRATION

In this connection it is also pertinent to inquire into the possible therapeutic value of intrabronchial injections of Besredka's antivirus in the treatment of chronic bronchitis and bronchiectasis since this may be related in some respects to the artificial stimulation of clasmatocytic phagocytosis.

Antivirus is prepared by cultivating the organism in a suitable broth medium for from eight to ten days followed by Berkefeld filtration. The filtrate is designated as "antivirus," and according to Besredka [5] contains something which is specifically bacteriostatic and bactericidal for the organism. That is to say, if the organism is replanted in the filtrate it either fails to grow or grows but sparsely, whereas other organisms grow almost as luxuriantly as in the control broth medium. Besredka stated that the inhibiting substance is specific, thermostabile and atoxic and for the want of a better term has called it antivirus. According to his experiments, it is possible to protect the lower animals against anthrax infection by first treating them with cutaneous applications of anthrax antivirus, and numerous experimental and clinical reports indicate that the application of wet dressings of staphylococcus and streptococcus antiviruses are of therapeutic value in the treatment of local staphylococcic and streptococcic infections. Since the results occur quickly, ordinarily in from twenty-four to forty-eight hours, Besredka expressed the opinion that antibody production is not involved, although he spoke of local cutaneous vaccination, while Gay [2] stated that the results are probably due to clasmatocyte stimulation.

---

5. Besredka, A.: Local Immunization by Specific Dressings, edited and translated by Plotz, Baltimore, Williams & Wilkins Company, 1927.

Be that as it may, there is no doubt that an organism planted in its antivirus fails to grow or grows but poorly even though it may retain its vitality and grow when subcultured into fresh broth. It may be that these effects are due to the exhaustion of specific pabulum, the accumulation of specific inhibitory metabolites, the production of specific inhibitory enzymes or the production of a virus identical with or related to what d'Herelle has designated as "bacteriophage." Here I am concerned with its probable value in the treatment of chronic bronchitis and bronchiectasis by intrabronchial injection, provided suitable experiments with rabbits indicate that it is nontoxic and safe for administration in this manner; an inquiry into its exact nature and mechanism of therapeutic activity will be left for further investigation. Indeed, Rosenthal [6] has already employed intrabronchial injections of antivirus in the treatment of bronchiectasis with alleged encouraging results.

BACTERIOPHAGE BY INTRABRONCHIAL ADMINISTRATION

Personally, I am inclined at present to the view that antivirus owes its therapeutic properties to stimulation of both microphagic and macrophagic phagocytosis along with local antibody production, but it may contain a principle directly destructive for the organism as Besredka maintains. If this is true, there may be a relationship between antivirus and bacteriophage as previously stated; at all events, it would appear profitable likewise to inquire into the possible therapeutic benefit to be derived from intrabronchial injections of bacteriophage in the treatment of chronic bronchitis and bronchiectasis.

The exact nature of the Twort-d'Herelle bacteriophage, however, is unknown at the present time; d'Herelle [7] maintained that it is a specific ultramicroscopic living virus capable of specifically destroying living bacteria. Others regard it as a bacterial enzyme, and while its nature is in dispute there is no doubt about the phenomenon of bacteriophagy in the test tube at least. That is to say, bacteriophage is sometimes derived from living organisms, and when the latter are subsequently planted from a stock culture in a solution of it they gradually undergo lysis. In other words, when living organisms are placed in antivirus they do not proliferate and may be recovered in a living state by subcultures; when placed in potent bacteriophage, they undergo destruction by lysis. Both are specific, that is to say, exhibit these effects only on the organisms used in the preparation of antivirus or bacteriophage, and while the effects are apparently dissimilar these may be due to

6. Rosenthal, G.: La cure de la dilatation des bronches et le rôle des injections intratrachéales et la trachéofistulisation emploi des boues antiseptiques, Paris méd. **1**:134, 1928.

7. d'Herelle, F.: The Bacteriophage and Its Behavior, translated by George H. Smith, Baltimore, Williams and Wilkins Company, 1930.

quantitative or other factors without necessarily involving two entirely different antibacterial substances.

However that may be, my primary interest in the present connection is the possible therapeutic value of intrabronchial injections of bacteriophage in the treatment of chronic bronchitis and bronchiectasis on the basis that if this were found safe and feasible by experiments on rabbits, therapeutic results may occur either by direct lysis of the infecting organisms, by stimulating microphagic and macrophagic phagocytosis or even by the local production of antibodies with special reference to opsonins.

At the outset, however, it was realized that bacteriophagic therapy involved considerable technical difficulty, especially in the preparation of suitable and potent bacteriophage for the streptococci recovered in cultures of bronchial secretions. Staphylococcus bacteriophage is easier to prepare, and that which is commercially available is frequently lytic for the staphylococci occurring in purulent bronchial exudates, but the preparation of bacteriophage for pneumococci has met with no success so far in my laboratory.

TOXICITY OF VACCINES, ANTIVIRUS AND BACTERIOPHAGE FOR RABBITS BY INTRABRONCHIAL INJECTION

Vaccines of Staphylococcus aureus and hemolytic streptococci recovered in cultures of bronchial secretions, containing approximately 1,000,000,000 heat-killed cocci per cubic centimeter and preserved with 0.3 per cent cresol, were extremely well borne by rabbits receiving as much as 1 cc. per kilogram of weight every two or three days for as many as twenty-four consecutive intrabronchial injections. In every instance the animals survived, maintained their weight and showed no demonstrable ill effects to either vaccine.

The same was true of a second series of rabbits receiving from six to twenty-four intratracheal injections of antiviruses of the same strains prepared by cultivating the organisms in a broth medium for ten days followed by Berkefeld filtration. As much as 1 cc. per kilogram of weight was injected every two or three days, and all animals survived without demonstrable ill effects.

Similar results were observed with bacteriophages for both strains injected intratracheally in a similar dose of 1 cc. per kilogram of weight every two or three days for a total of from six to twenty-four consecutive injections, so that it may be stated that these substances were well borne by normal rabbits by this route of administration despite the fact that the doses were purposely made extremely large according to body weight. It is true that the injections were sometimes followed in a few hours by a temporary elevation of rectal temperature along with slight but definite leukocytosis, especially in those animals receiving

intrabronchial injections of the two vaccines, but these changes were usually observed only after the first to the third injection, following which it appeared that the animals rapidly acquired tolerance for all three products of each organism.

Furthermore, the injections did not appear to produce more than slight amounts of bronchial exudates. Autopsy was performed several days after the last of six, twelve and twenty-four injections of each product, and the lower portion of the trachea and of the bronchi were carefully inspected along with the preparation of smears from numerous locations for cytologic examination, but in no instance were there any macroscopic evidences of pronounced bronchitis resulting from irritation due to any of the products administered.

The smaller bronchi, however, frequently contained more exudate than was found in untreated controls and especially in those rabbits receiving intrabronchial injections of the two vaccines; smears stained with methylene blue (methylthionine chloride, U. S. P.), hematoxylin and eosin and neutral red showed the presence of increased numbers of not only polymorphonuclear leukocytes but likewise of the larger cells corresponding to descriptions of the morphologic and staining characteristics of clasmatocytes. These cytologic changes were most marked, however, in smears of secretions from rabbits receiving injections of the vaccines and antiviruses, but were practically absent or much less in evidence in smears taken from animals receiving the injections of the two bacteriophages.

PATHOLOGIC TISSUE CHANGES

Sections for histologic examination were also prepared from the trachea above the bifurcation, the lungs and kidneys of all animals.

So far as the trachea and larger bronchi are concerned, there were practically no pathologic changes beyond a slight degree of hyperemia with slight edema in the submucosa of an occasional animal and especially among those receiving injections of the two vaccines.

The smaller or terminal bronchi, however, sometimes showed slight but definite histologic evidences of irritation characterized by the presence of exudates on the mucosa with small peribronchial areas of cellular infiltration. The ciliated epithelium of the mucosa, however, appeared to be intact in all instances. Of course, the cellular infiltrations of the submucosa and surrounding alveoli commanded most attention, and these appeared to be composed largely of polymorphonuclear leukocytes and lymphocytes, but in many instances examination with high magnification showed larger cells which may have been clasmatocytes. Unfortunately, I could not be sure of their identity in the sections, and vital staining for their more definite identification was not employed.

At any rate, it was evident that intrabronchial injections of the vaccines, antiviruses and bacteriophages were well borne by all of the animals but with slight histologic evidences of irritation, although the bronchi, particularly the smaller divisions, showed slight but definite evidences of increased cellular exudation, especially in the case of the animals receiving intrabronchial injections of the vaccines and antiviruses. These changes, however, were not uniformly distributed through the lungs but were more apparent in the right lungs and especially in the lower lobes, probably because of a wider distribution of the inocula in these locations. In no instance were there any evidences of bronchopneumonia or severer injury with abscess production, as is sometimes observed following intrabronchial injections of chemical agents previously described,[1] and the kidneys of all animals presented no macroscopic or microscopic evidences of injury.

ANTIBODY PRODUCTION BY INTRABRONCHIAL IMMUNIZATION

Preliminary opsonic and agglutination tests were made of the blood of all animals before the injections were given and repeated at intervals throughout the period of from six to twenty-four treatments. The phagocytic and opsonic indexes showed a distinct increase, especially well marked among the rabbits receiving the staphylococcus and streptococcus vaccines, although well defined individual variations in antibody response among the animals has not permitted anything more than a general statement. These results were definite in the majority of the animals after the second intrabronchial injection, while in others the effects were not clearly demonstrable until after as many as four injections had been given.

All of the animals receiving intrabronchial injections of the two antiviruses also showed an increase of opsonin for both organisms, but in general terms the amount was somewhat less than that observed in the rabbits receiving the vaccines, while the amount observed was still less in those receiving the injections of the two bacteriophages. While marked individual variations occurred, it would appear that the vaccines were most antigenic in this particular and the bacteriophages least antigenic.

Similar results were observed in agglutinin production for both organisms. These tests were technically more satisfactory and the reactions sharper and more definite. Here again the vaccines and antiviruses appeared to be more antigenic than the bacteriophages, and all three of the staphylococcus products were more antigenic than those prepared of the streptococci; furthermore, the agglutinins appeared more tardily, especially those for the streptococci, which in some instances were not definitely demonstrable until after as many as five injections had been given.

The results have clearly shown that intrabronchial injections of staphylococcus and streptococcus vaccines, antiviruses and bacteriophages result in the production of specific opsonins and agglutinins in normal rabbits.

ACQUIRED PROTECTION BY INTRABRONCHIAL IMMUNIZATION

Additional experiments were conducted in an attempt to determine whether intrabronchial injections of vaccines and antiviruses of virulent Staphylococcus aureus, a hemolytic streptococcus and a type I pneumococcus afforded any protection against intrabronchial injections of broth cultures of these organisms.

The vaccines of all three organisms were prepared by cultivating them in a suitable broth medium for three days followed by sterilization with 0.3 per cent cresol. They represented vaccines of chemically killed organisms along with such toxins as were produced during an incubation of three days.

The antiviruses were prepared by cultivating the organisms in broth for ten days followed by Berkefeld filtration and subculturing for sterility.

The dose of each vaccine and antivirus was 1 cc. per kilogram of weight administered by intratracheal injection every two days for from three to six injections.

Controls received intratracheal injections of the sterile broth medium in the same dosage and manner and at the same time as did the experimental animals.

Especially definite evidence of acquired immunity to the type I pneumococcus was observed after as few as three intrabronchial injections of the pneumococcus vaccine and antivirus. For example, the intratracheal injection of 0.5 cc. of ten hour harmone broth cultures [1] of this pneumococcus into control rabbits resulted in a fatal septicemia of all with positive cultures of the heart blood within forty-eight hours after inoculation. The same was true of rabbits inoculated intratracheally after receiving from two to three intrabronchial injections of sterile broth, indicating that the broth alone was without demonstrable protective value against this highly virulent pneumococcus injected intratracheally. But all of the animals receiving the intrabronchial injections of the vaccine survived when given injections with the virulent pneumococcus, as was likewise true of all animals receiving three injections of the antivirus. These results, therefore, afforded definite evidence of the fact that intrabronchial injections of type I pneumococcus vaccine and antivirus resulted in immunization against fatal infection by intratracheal inoculation with the organism, and since intrabronchial

1. Broth culture medium, presumably containing vitamins or harmones derived from living tissue and, therefore, favorable to bacterial growth.

injections of sterile broth were without these effects it is apparent that the presence of the pneumococcus and its products in the vaccine and antivirus produced specific effects.

Less definite evidence, however, was secured in the case of the staphylococcus and streptococcus owing to the fact that both organisms were much less virulent for rabbits by intratracheal inoculation.

Only from 20 to 50 per cent of the controls inoculated intratracheally with large amounts of twenty-four hour harmone broth cultures (2 cc.) succumbed with septicemia, as was likewise true of controls receiving three preliminary intrabronchial injections of sterile broth for nonspecific mobilization of microphagic and macrophagic phagocytes including clasmatocytes. However, all animals receiving three preliminary intrabronchial injections of the staphylococcus and streptococcus vaccines and antiviruses survived when inoculated intratracheally with 2 cc. amounts of twenty-four hour harmone broth cultures of the respective organisms and thereby indicated some degree of acquired immunity; but since some of the controls likewise survived, the results were not as definite as those observed with the type I pneumococcus.

However, it was apparent that as few as three intrabronchial injections of vaccines and antiviruses of Staphylococcus aureus, a hemolytic streptococcus and a type I pneumococcus resulted in engendering demonstrable degrees of acquired immunity to the three organisms which was especially well marked in the case of the pneumococcus.

PRACTICAL APPLICATIONS

I am convinced, therefore, that it is both safe and feasible to try intrabronchial injections of autogenous vaccines, antiviruses and bacteriophages in the treatment of the chronic intractable bronchitides, bronchiectasia and other types of suppurative pneumonitis of man.

Certainly it would appear from these experiments with rabbits that all three substances are extremely well borne by intrabronchial injection and that their administration by this route may be of therapeutic benefit.

Autogenous vaccines and antiviruses are especially interesting in this connection because of the ease of preparation in the large amounts likely to be required. The preparation of bacteriophage is much more difficult and indeed may be impossible for some of the bacteria secured in cultures of bronchial secretions. Staphylococcus bacteriophage is ordinarily readily prepared and may be obtained commercially, but the preparation of streptococcus and pneumococcus bacteriophages may be difficult and indeed impossible so far as the preparation of the large amounts of actively lytic products are concerned. Furthermore, bacteriophages should not be tried until actual preliminary tests have shown that they are actively lytic in the test tube for the organisms against which they are to be employed. I believe that intrabronchial injections

of actively lytic phages may be of therapeutic benefit, but the technical difficulties of preparation may constitute an objection to their use on a large scale.

Autogenous vaccines, however, are readily prepared in large amounts, and for this purpose I suggest that bronchial secretions be secured bronchoscopically in the Tucker, Clerf or other collectors and cultured in flasks of harmone broth medium suitable for the cultivation of streptococci. These may be incubated for about five days, at the end of which time fairly heavy growths will be observed. In many instances these are almost pure cultures of streptococci, but in the majority of such cultures staphylococci, pneumococci and various gram-positive and gram-negative organisms also occur with streptococci predominating. The mixed culture, however, should be used and may be diluted with sterile saline solution to give a total concentration of about 1,000,000,000 organisms per cubic centimeter. Cresol may now be added to give a total concentration of 0.5 per cent (10 cc. of a stock 5 per cent solution to each 100 cc. of vaccine), well mixed and incubated at 37 C. for twenty-four hours when subcultures are made for sterility. This type of vaccine contains the broth and approximately 1,000,000,000 chemically killed organisms per cubic centimeter along with their exogenous toxins and, in my opinion, is to be preferred to the usual heat-killed suspensions in saline solution in order to secure the effects of the broth alone in the mobilization of both microphages and macrophages with special reference to clasmatocytes in the bronchial exudates and in the bronchial tissues for purposes of phagocytosis.

Antivirus may be prepared in exactly the same manner, except that the culture of bronchial secretions in broth is cultivated at 37 C. for ten days followed by Berkefeld filtration. The clear filtrate should then be cultured for sterility and put in sterile vials or flasks in the amounts required for treatment without the addition of a preservative.

Only future clinical trial can determine the relative therapeutic effectiveness of vaccine and antivirus; personally, I expect results from both and especially from the latter.

The method of administration and dosage must likewise be determined by clinical trial and experience, but I would suggest that the ropy, mucoid secretions first be removed by lavage with the Bledsoe-Fisher hypertonic saline solution by the method of Stitt [8] before introducing vaccine, antivirus or bacteriophage. According to this method, 15 cc. of saline solution is slowly forced through a catheter into the bronchi coincidentally with each inspiration, followed by expulsion along with the thick ropy secretions until as much as 250 cc. is used. Following the last

8. Stitt, H. L.: Bronchial Aspiration and Irrigation with a Hypertonic Saline Solution, J. Med. **8**:112 (May) 1927.

washing, the vaccine, antivirus or bacteriophage may be introduced.

The initial dose may be about 5 cc. in order to have it retained with as wide distribution as possible. If well borne, the treatments may be given about twice a week and the doses gradually increased. Larger doses are particularly indicated if bacteriophage is employed. It may be that the doses of vaccine and antivirus must vary for individual cases according to the amounts of toxin present, since it is likely that both contain variable amounts of toxin which will vary with different cultures, especially in the cases of streptococci and staphylococci.

When vaccine or antivirus is employed there may be an added advantage in using one of the chemical disinfectants for lavage as suggested in the preceding paper [1] of this series instead of the plain saline solution. Indeed, this would appear to be the better procedure in order to secure the possible benefit of chemical disinfection, especially since the disinfectants and solutions recommended are without injurious effects on the bronchi and phagocytes; but if bacteriophage is employed, the disinfectants should be omitted in the lavage because they may destroy the bacteriophage if the latter is indeed a living virus.

SUMMARY

1. Phagocytosis is apparently the principal mechanism of defense and recovery in chronic bronchitis, bronchiectasis and other types of suppurative pneumonitis.

2. In this connection phagocytosis by cells of the macrophage system with special reference to clasmatocytes would appear to be of special importance.

3. Any therapeutic procedure promoting phagocytosis of the streptococci, staphylococci and other organisms in the bronchial secretions of suppurative pneumonitis will likely prove of therapeutic value.

4. In this connection is suggested the administration of autogenous vaccines and antiviruses by intrabronchial injection for the purpose of mobilizing phagocytes, stimulating phagocytosis and promoting local and general antibody production.

5. Intrabronchial injections of antivirus may also produce direct destruction of infecting organisms in addition to promoting macrophagic phagocytosis and antibody production.

6. Intrabronchial injections of bacteriophage may result in the direct destruction of living organisms as well as stimulate phagocytosis.

7. Intrabronchial injections of staphylococcus and streptococcus vaccines, antiviruses and bacteriophages have been extremely well borne by rabbits in doses of 1 cc. per kilogram of weight every two days for from six to twenty-four injections.

8. Intrabronchial injections of vaccines, antiviruses and bacteriophages, and especially of vaccines and antiviruses, have increased the number of microphages and macrophages in the bronchial secretions of rabbits.

9. Intrabronchial injections of vaccines and antiviruses have produced an increase of opsonins and agglutinins in the blood of rabbits.

10. Intrabronchial injections of vaccines and antiviruses of type I pneumococcus, hemolytic streptococcus and Staphylococcus aureus have increased the resistance of rabbits to intratracheal inoculations of virulent cultures, especially in the case of type I pneumococcus.

11. On the basis of these results, it is suggested that the treatment of chronic bronchitis, bronchiectasis and other types of suppurative pneumonitis by bronchial lavage and intrabronchial injections of autogenous vaccines, antiviruses and bacteriophages is worthy of clinical trial.

12. Methods are suggested for the preparation of vaccine and antiviruses and their administration by intrabronchial injection alone or in combination with bronchial lavage with chemical disinfectants.

EXPERIMENTAL EDEMA IN NEPHRECTOMIZED DOGS

III. SERUM PROTEINS AND EFFUSION FLUIDS

C. J. FARMER, M.A.

F. S. BARRY, M.S., M.B.

ALICE REED, M.S.

AND

A. C. IVY, M.D.

CHICAGO

Lyon, Shafton and Ivy [1] found that subcutaneous administration of Ringer's solution prolonged the life of bilaterally nephrectomized dogs, and produced a general anasarca, frequently with ascites, hydrothorax and hydropericardium. Barry and Ivy [2] studied the mechanism of the edema and found that edema does not result until water with excessive sodium chloride is supplied, and that retention of urinary products per se in the presence of hypochloremia is not conducive to edema even when adequate water is supplied in the form of 4 per cent dextrose solution.

The objects of the present study were: first, to observe the changes in serum proteins, and second, to determine the protein content of effusion fluids with the hope that the results might throw further light on the mechanism and type of the edema, and establish some correlation between this experimental edema and some form of clinical edema.

METHODS

Only large, well nourished dogs of about 20 Kg. body weight were employed as experimental animals. The kidneys were removed with strict aseptic precautions and with practically no loss of blood. Beginning on the day after the operation, the dogs were aseptically inoculated subcutaneously with from 1,500 to 2,000 cc. of Ringer's solution per day in 500 or 750 cc. doses, the amount varying with the weight of the dog (about 90 cc. per kilogram). The dogs were allowed water ad libitum and were fed as long as they would eat a diet of bread, yellow corn meal and bone soup. Blood samples were taken daily for chemical studies,

From the Department of Physiology and Pharmacology and the Department of Biochemistry, Northwestern University Medical School.

1. Lyon, E. E.; Shafton, A. L., and Ivy, A. C.: Prolongation of the Life of Nephrectomized Dogs with the Production of Edema, Arch. Int. Med. **44**:424 (Sept.) 1929.

2. Barry, F. S.; Shafton, A. L., and Ivy, A. C.: Experimental Edema in Nephrectomized Dogs: II. The Rôle of Water and Chloride, Arch. Int. Med. **51**:200 (Feb.) 1933.

and the time of occurrence of visible edema was closely noted. The effusion fluid was collected either immediately after death or within two hours. Other pathologic changes were noted at postmortem examination. Occasionally, the pericardial and ascitic fluid was blood-tinged, even though no bleeding point could be found.

Robertson's microrefractometric method [3] was employed to determine the concentration of serum proteins. Although this method had been used previously by Rowe,[4] in a study of protein partition in nephritic serum, and found satisfactory, it seemed desirable to check our values against those obtained on the same serum using chemical methods. For this purpose, serum globulin was precipitated by a 22.2 per cent sodium sulphate solution at 37 C., as suggested by Howe,[5] and the method of Koch and McMeekin [6] was used to determine total nonprotein nitrogen and protein nitrogen in the filtrates and diluted serum. From these values the protein partition was calculated. The quantities estimated by both methods are in general agreement, with the exception of the amount on the seventh day for dog 6. We have no explanation for this single discrepancy, as both sets of determinations were repeated with satisfactory checks. From these results, we feel that conclusions based on values reported in this paper are independent of the method of analysis.

EXPERIMENTAL DATA

The material for this series of experiments consisted of thirteen bilaterally nephrectomized dogs, three untreated controls and ten receiving daily subcutaneous injections of Ringer's solution. Two of the controls and three treated dogs were rejected on account of distemper. One treated dog showed blood in the ascitic fluid at autopsy. This was found to be due to the failure of the peritoneum to heal at the site of the wound. The dog was thereupon rejected.

Chart 1 *A* is a graphic indication of the day-to-day serum protein partition of a typical treated dog (dog 6). It will be noted that there is a marked decrease in total serum protein. The albumin fraction falls rapidly, while the globulin after an initial drop shows a marked increase. Reversal of the albumin and globulin fractions occurred in all cases on the fourth or fifth day after operation. Edema developed in four of six animals on the day previous to that on which the albumin-globulin reversal occurred. The concentration of nonprotein substances increased in all cases, but to a less degree than in the untreated control. The small curve in chart 1 *B* is reproduced from the paper of Barker and Kirk.[7] Using plasmapheresis, they noted an increase in globulin as the albumin fraction was lowered. Edema (of the nephrosis type) in their

3. Robertson: J. Biol. Chem. **22**:233, 1915.

4. Rowe, A. H.: Refractometric Studies of Serum Proteins in Nephritis, Cardiac Decompensation, Diabetes, Anemia, and Other Chronic Diseases, Arch. Int. Med. **19**:354 (March) 1917.

5. Howe: J. Biol. Chem. **49**:109, 1921.

6. Koch and McMeekin: J. Am. Chem. Soc. **46**:2066, 1924.

7. Barker, M. H., and Kirk, E. J.: Experimental Edema (Nephrosis) in Dogs in Relation to Edema of Renal Origin in Patients, Arch. Int. Med. **45**:319 (March) 1930.

dogs appeared when the serum albumin reached a value of approximately 0.8 per cent. As will be seen from this and later charts, edema developed in our animals at a higher albumin concentration. Furthermore, we found no relationship between the percentage of serum albumin and the appearance of edema.

The maintenance of normal plasma chlorides during the investigation is shown in table 1. A few comments as to the physical condition of the dog during the experiment are included.

The data from which the graph for dog 6 (chart 1) was constructed are shown in table 2. We include the data on dog 6 because they are

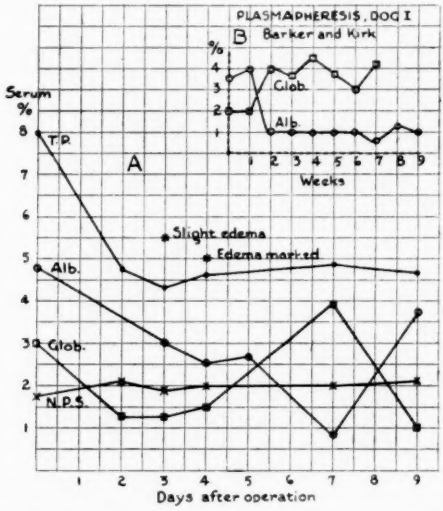


Chart 1.—*A*, day-by-day serum protein partition in dog 6. Note that the albumin-globulin ratio may be reversed in the presence of edema. In charts 1 and 2, *T. P.* = total serum protein; *Alb.* = albumin; *Glob.* = globulin, and *N. P. S.* = nonprotein substances. *B*, plasmapheresis in a dog (from Barker and Kirk[7]).

typical and the animal lived the longest. The lower part of the table presents data obtained on analysis of the effusion fluids. It is important to note the high protein content of all fluids. Additional data on effusion fluids are given in table 4.

Table 3 presents data relative to serum protein levels at the onset of edema. It will be noted that edema appeared in three of six dogs on the fourth day after operation. These animals showed the highest serum albumin percentages of the group, and in each case the albumin concentration was greater than that of globulin. The albumin-globulin

TABLE 1.—*Saline Solution Therapy and Blood Chlorides (Dog 6)*

Date	Ringer's Solution Injected, Cc.	Blood Chlorides, Mg. per 100 Cc.	Comment
2/ 3/30	0	482.9	Prior to operation
2/ 4/30	1,500	445.7	
2/ 5/30	1,500	402.3	Slight vomiting
2/ 6/30	1,750	.....	Slight edema in forelegs; vomiting
2/ 7/30	1,750	487.6	Marked edema in all legs; vomiting
2/ 8/30	2,000	490.9	Marked edema, including belly and scrotum; slight diarrhea and vomiting
2/ 9/30	2,000	514.7	Edema extended to face; severe vomiting; slight diarrhea
2/10/30	1,750	510.7	Marked edema of face; severe vomiting, salivation; slight diarrhea; formed stools
2/11/30	1,750	511.2	Marked general edema, extending to lips and tongue; vomiting; formed stools; noticeable weakness
2/12/30	1,750	504.6	Marked general edema, extending to back of head and base of ears; profuse vomiting; slight diarrhea; marked weakness and difficulty in standing
2/13/30	.....	.....	Died in early morning; no pneumonia; wet lungs; general anasarca

TABLE 2.—*Analysis of Blood and of Effusion Fluids (Dog 6)*

Date	Nonprotein Substances, per Cent	Total Proteins, per Cent	Albumin, per Cent	Globulin, per Cent
	Venous Blood			
2/ 3/30 (preoperative)	1.93	7.81	4.77	3.04
2/ 5/30	2.12	4.81	3.48	1.33
2/ 6/30	1.88	4.40	3.06	1.34
2/ 7/30	1.98	4.58	3.12	1.46
2/10/30	1.98	4.74	0.78	3.96
2/12/30	2.11	4.64	3.64	1.03
2/13/30	Effusion Fluids			
Ascitic fluid (1,800 cc. clear straw color)	2.17	1.487	0.837	0.650
Pericardial fluid (15 cc. clear yellow)	2.45	1.296	1.130	0.166
Pleural fluid (slightly reddish color; right cavity, 35 cc.; left cavity, 40 cc.)	2.17	1.257	0.973	0.284

TABLE 3.—*Serum Protein Level at Onset of Edema*

Dog	Days after Operation	Nonprotein Substances, per Cent	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent
1	4	2.51	6.13	3.29	2.84
2	3	2.08	4.39	2.62	1.77
3	4	2.56	5.52	4.24	1.28
4	5	2.46	4.53	2.02	2.51
6	4	1.98	4.58	3.12	1.46
7	6	2.16	4.85	1.82	3.03

reversal was noted in dog 1 on the day following the onset of edema. In dog 6, blood drawn the third day following the onset of edema showed extreme reversal (globulin, 3.96 mg. per hundred cubic centimeters, and albumin, 0.78 mg.). Our data on dog 3 indicate that had the animal lived (it lived about six days) reversal would have occurred before the second day following the appearance of edema. In dog 2 edema developed, with the proportion of albumin higher than that of globulin. Serum analyzed on the following day showed approximately equal concentrations of each constituent. The animal died (after five days) before another sample of blood could be obtained. In dogs 4 and 7

TABLE 4.—*Analysis of Effusion Fluids and Heart Blood*

Dog	Type of Fluid	Nonprotein Substance, per Cent	Total Protein, per Cent	Albumin, per Cent	Globulin, per Cent
2	Ascitic	3.86	3.245	2.000	1.245
	Pericardial	2.51	2.437	0.847	1.590
	Last blood before death	2.26	4.220	2.14	2.080
3	Ascitic	3.29	.....	3.53	.....
	Pericardial	3.29	.....	3.28	.....
	Heart blood	3.15	5.484	5.34	0.144
	Last blood before death	2.88	5.230	2.88	2.350
4	Ascitic	2.70	.....	1.65	.....
	Pericardial	2.75	.....	1.85	.....
	Heart blood	2.90	4.380	4.23	0.157
	Blood one hour before death	2.85	.....	5.54	.....
6	Ascitic	2.17	1.487	0.837	0.650
	Pericardial	2.45	1.296	1.130	0.166
	Pleural	2.17	1.257	0.973	0.284
	Last blood before death	2.11	4.640	3.540	1.030
7	Ascitic	2.74	.....	.....	.....
	Pericardial	2.90	1.866	0.406	1.460
	Heart blood	2.95	4.520	2.080	2.440
	Last blood before death	2.85	4.630	2.010	2.620

edema developed on the fifth and sixth days respectively after operation. In both cases the serum globulin was higher than the albumin. Dog 4 survived for more than two days, and dog 7 for more than three days after the appearance of edema. Since edema developed in dog 6 before the albumin-globulin reversal occurred, and the animal survived for over five days, it is impossible from the present data to draw conclusions suggesting a relationship between serum albumin and serum globulin values at the appearance of edema and during survival periods. There is probably no such relation.

Table 4 presents data on the composition of the effusion fluids; for comparison, figures representing the values of the various constituents in venous blood drawn from one to twenty-four hours prior to death are included. In three cases serum was obtained from heart blood drawn at autopsy (shortly after death). The uniformly high concentration of non-

protein substances in all effusion fluids is striking. In one instance the values are greater than those recorded for the serum of the last blood obtained before death. The concentration of total protein in the various effusion fluids, although high in all cases, is lower than that of blood serum. Of the effusion fluids the protein content is highest in the ascitic, with that of the pericardial and pleural fluids decreasing in the order named. These observations are in agreement with those reported by Loeb, Atchley and Palmer,[8] who studied in patients the equilibrium between blood serum and serous cavity fluids. It is seen, furthermore, that the proportion of albumin to globulin in effusion fluids bears a general relationship to their partition in blood serum. Dogs 6 and 7 illustrate this. From the analytic data available, it is seen that the percentages of albumin and globulin in effusion fluids of dogs 2 and 3 were greater than in dogs 6 and 7. The survival period after the appearance of edema in dogs 2 and 3 was less than two days, while dogs 6 and 7 lived between five and six, and between three and four, days respectively. Dog 4 survived about three days after edema developed and showed an albumin content intermediary between the values of the aforementioned groups.

Chart 2 presents data on an untreated control animal (dog 13) and on a dog in which distemper developed during treatment. Note in dog 13 (graph A) early reversal of serum albumin and globulin curves. The globulin rose to 5.5 per cent on the fourth day after operation, a value much higher than that attained by any treated dog in the series. The albumin dropped rapidly for three days, and then before death increased sufficiently in concentration to elevate the total protein to a high figure. Nonprotein substances increased more rapidly than in treated dogs. Notwithstanding this change in the blood protein picture, edema failed to develop.

In the graph for dog 10 (chart 2B), it will be seen that the amount of serum globulin was greater than that of albumin at the day of operation. This reversal occurred before any clinical manifestation of distemper appeared. Distemper was observed on the day after the operation. This dog received subcutaneous injections of Ringer's solution daily, but it died of distemper, and edema failed to develop. In this case, the daily injection of saline solution could not prolong life sufficiently for edema to develop.

In a second group of five experiments the nephrectomized dogs received injections of a mixture of two-thirds 4 per cent dextrose and one-third Ringer's solution, which was known [2] to prolong life but not

8. Loeb, Atchley and Palmer: J. Gen. Physiol. **4**:591, 1922.

to produce visible edema. Edema did not develop in these dogs. The nonprotein nitrogen in the serum was increased, the total serum protein was decreased, and the albumin-globulin ratio was reversed. Work by Miss Reed and Professor Farmer to be published in detail later shows that the blood potassium, sodium and calcium values remain constant. The phosphorus is increased. In control nephrectomized dogs the amounts of sodium, potassium and calcium in the blood are slightly increased, owing to concentration of the blood. Phosphorus is markedly increased. Table 5 shows the results of a typical analysis of the blood.

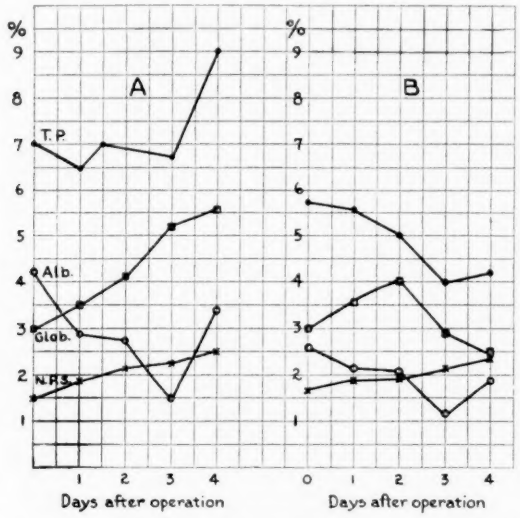


Chart 2.—*A*, data on an untreated control dog (dog 13). *B*, data on a dog (dog 10) treated with Ringer's solution, in which distemper resulted on the day following the operation.

TABLE 5.—*Chemistry of Blood Serum*

Days After Operation	Nonprotein Substances, per Cent	Total Protein, per Cent	Sodium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Chloride, Mg. Sodium Chloride per 100 Cc.
Dog 11 (Injected Dextrose 2/3 plus Ringer's Solution 1/3; no edema produced)							
0	1.25	6.30	346.33	....	13.04	....	483.2
2	2.21	5.78	344.33	21.0	.....	7.89	.....
3	2.36	5.50	.....	....	11.34	6.41	492.3
4	1.82	5.06	313.33	29.5	13.23	7.65	.....
6	1.93	4.92	306.50	30.0	13.23	11.03	487.6
7	1.98	4.07	305.17	30.5	.....	11.36	.....
8	2.14	4.07	281.84	31.5	12.29	15.00	504.5
Dog 16 (Untreated Control)							
0	1.25	7.36	308.83	22.0	14.45	1.55	
1	1.64	6.87	347.50	25.0	16.50	2.50	
2	2.57	6.68	351.83	32.0	15.80	2.90	
3	2.57	6.48	.....	33.0	16.10	3.85	
4	2.21	7.01	365.00	32.0	.....	4.70	
5	2.31	7.41	350.83	33.0	19.75	5.20	

COMMENT

Leiter [9] and Barker and Kirk [7] have produced edema in dogs by inducing hypoproteinemia by the method of plasmapheresis. They were stimulated to perform such experiments by the consistent occurrence of a low plasma protein level in patients with renal edema who were excreting albumin in the urine. Leiter reported that when the plasma proteins had fallen to 3 per cent or less in his dogs, edema occurred. The effusion fluid in Leiter's dogs had a protein content of less than 0.25 per cent and often below 0.1 per cent. Barker reported that "it was impossible to foretell the time of appearance and amount of edema by the total protein level" and expressed the belief that an unusually low albumin content of 0.8 Gm. per hundred cubic centimeters was more indicative of the "edema level." He found, further, that a low protein content caused pathologic changes in the renal parenchyma. There was no increase in the blood nonprotein nitrogen in his dogs. The picture presented by Barker's dogs along with the low protein content of the effusion fluid found by Leiter suggests that the edema they produced was comparable to the edema that occurs in "nephrosis" which is sometimes included under the term "chronic parenchymatous nephritis." [10]

The experimental conditions and findings in our dogs are quite different from those of Leiter and Barker. Any change that occurred in our dogs was certainly extrarenal, since the kidneys had been removed. Any change that occurred was due to absolute acute renal insufficiency. We administered water, which in itself does not cause edema, and sufficient chlorides in a "physiologic ratio" to keep the blood chlorides normal, and edema resulted. However, chlorides (most probably sodium chloride) must be administered in excess of the requirements of the body, since edema does not develop in dogs given a mixture of dextrose and Ringer's solution. Our dogs showed a high grade urinary retention with changes in the blood serum protein and a decrease in total protein. The protein content of the effusion fluid was high, which probably denotes an increased capillary permeability, since the protein content of normal peritoneal fluid, according to Vogt,[11] is rarely above 0.7 per cent. These findings are comparable to those in acute glomerular nephritis in man in which there is urinary retention associated with a high protein content (1 per cent) of the effusion fluid according to Beckman,[12] whereas the protein content of the effusion fluid in Leiter's dogs was not more than 0.25 per cent. Our data on the protein content

9. Leiter, L.: Proc. Soc. Exper. Biol. & Med. **26**:173, 1928.

10. McLean: Physiol. Rev. **5**:634, 1925. Loeb, Atchley and Palmer.[8]

11. Vogt, E.: Arch. f. Gynäk. **120**:40, 1923; Med. Klin. **19**:943, 1923.

12. Beckman: Deutsches Arch. f. klin. Med. **135**:39, 1921.

of the effusion fluid are comparable to those found by Kumpf,[13] who observed edema in two rabbits following repeated hemorrhage, the kidney of one being essentially normal and of the other showing some spontaneous degenerative changes on histologic examination. (In this connection the studies of Loeb[14] and Govaerts[15] on peritoneal absorption and on the protein content of the effusion fluid in uranium nephritis are interesting, but not directly apropos.) Since our dogs were not losing blood protein through the urine and it was not being removed by us, there are only two possible processes which can have occurred to reduce it, one being that it passed out into the tissue fluids and the other that it was metabolized and not replaced. The former is more likely, since we found a high protein content of the effusion fluid, and since starvation has little effect on blood proteins. The decrease in blood protein was probably not due to plasma volume, since our hematocrit readings show only a slight increase in plasma volume. Whereas plasmapheresis produces edema which may be comparable to that occurring in nephrosis, the type observed in our nephrectomized dogs, we believe, more closely simulates the edema accompanying acute glomerular nephritis in man.

The total serum protein was not reduced in untreated nephrectomized dogs, but only in the dogs which received Ringer's solution. The reduction in total serum protein in the treated dogs may have played a rôle in the production of edema. Whether this is cause or effect cannot be stated from the data. The total serum protein fell before visible edema developed. That the reduction of total serum protein is not the sole factor in the mechanism of the edema observed in our nephrectomized dogs is shown by the fact that in nephrectomized dogs receiving a mixture of two-thirds 4 per cent dextrose and one-third Ringer's solution, the serum protein decreased, but edema did not result, the water input being the same and the sodium chloride input reduced. Even in the low proteinemic edema (plasmapheresis) experiments of Leiter and Barker, sodium chloride was an important factor. That low total protein is not the sole factor agrees with the observations of Linder, Lundsgaard and Van Slyke[16] in patients who found serum proteins reduced in the nephrotic type of nephritis, whether or not edema was present. They concluded that although a low protein concentration and edema frequently occur together, their relationship is not a simple

13. Kumpf, A. E.: Experimental Edema and Lipemia Produced by Repeated Bleeding, Arch. Path. **13**:415 (March) 1932.

14. Loeb, Leo: Edema, Baltimore, Williams & Wilkins Company, 1923.

15. Govaerts: Bull. Acad. roy. de méd. de Belgique **8**:33, 1928.

16. Linder, Lundsgaard and Van Slyke: J. Exper. Med. **39**:887 and 921, 1924.

one of cause and effect. In our dogs with acute renal insufficiency and lowered serum protein and with water administered to more than compensate for thirst, edema did not develop until salt was added, and the amount of edema was roughly proportional to the amount of salt administered.

Although it logically follows from our observations that restriction of sodium chloride should prevent edema from occurring in acute renal insufficiency, it does not follow that the edema in all patients should be cleared up solely by this restriction, because the mechanism of water balance in some patients may become more or less stabilized, and a nitrogen or protein deficiency may have to be satisfied or the sodium ion replaced by the potassium, calcium or ammonium ion before a normal water balance may be established.

CONCLUSIONS

1. Edema developed in four of six animals on the day previous to the albumin-globulin reversal.

2. No relation between the amount of serum albumin and the appearance or presence of edema was evident in treated dogs in which edema developed.

3. Distemper may reverse the albumin-globulin ratio, and the ratio may be reversed in untreated dogs in which edema does not develop and the total serum protein remains fairly constant.

4. Reversal of the serum albumin-globulin ratio has no direct relation to the development of edema.

5. The total serum protein is not reduced in untreated nephrectomized dogs. It is reduced, however, in nephrectomized dogs treated with Ringer's solution. Whether this is a cause or an effect cannot be stated from the data. The total serum protein falls before visible edema occurs. That the reduction in total serum protein is not the sole factor in the mechanism of the edema observed in our dogs is shown by the fact that in nephrectomized dogs receiving a mixture of two-thirds 4 per cent dextrose and one-third Ringer's solution, the serum protein decreased but edema did not result, the water input being the same and the chloride input reduced. We do not doubt that the reduction in total serum protein is a contributory factor, or may be an essential factor, but sodium chloride, or sodium, is certainly an essential factor.

6. The effusion fluids of nephrectomized dogs treated with Ringer's solution have a total protein content ranging from 1.3 to 4 per cent, which is in marked contrast to the effusion fluids in edema produced by repeated plasmapheresis. The greater protein content, we believe, indicates that acute urinary retention increases capillary permeability.

CARDIOSPASM

WITH A REVIEW OF THE LITERATURE

MILLS STURTEVANT, M.D.
NEW YORK

In collecting data for teaching purposes regarding mega-esophagus, I was impressed with the lack of any full account of this condition in English. Thieding's [1] monograph, the outstanding contribution on this subject to date, published in German in 1921, contains nothing of the work of Plummer and Vinson, not to mention other important American or British writers. Beside this, Thieding's paper is given over to an attempt to prove that cardiospasm is a part of autonomic imbalance and that as such it is symptomatic of psychoneurosis. It has therefore seemed worth while to connect and publish my notes, using Thieding's paper freely and referring to his large bibliography, exhaustive, doubtless, within the limits of the literature available to that author at that time. Data collected from 13 personally observed cases, during five years of existence of the group service of gastro-enterology in the New York University division of Bellevue Hospital, will be given.

Cardiospasm has been given different names by different observers, the choice of name depending in most instances on the observer's conception of the cause or the pathology. Achalasia of the cardia, simple ectasia of the esophagus, mega-esophagus, preventriculosis, spindle-shaped dilatation of the esophagus and idiopathic dilatation of the esophagus are to be found in use in the literature on the subject.

DEFINITION

Cardiospasm is the common name used for a condition in which, without a demonstrable obstructive pathologic change, and usually without pain, food does not pass readily from the esophagus into the stomach, but is held in the esophagus, which, in the majority of cases, undergoes dilatation, sometimes extreme.

HISTORICAL DATA

Spastic conditions of the esophagus have been recognized since 1733, when F. Hoffmann published "de spasmis gulae inferioris et de nausea,"

From the Department of Medicine, the University and Bellevue Hospital Medical College, New York University, and the Third Medical Division, Bellevue Hospital.

1. Thieding, F.: Ueber Cardiospasmus, Atonie und idiopathische Dilatation der Speiseröhre, Beitr. z. klin. Chir. **121**:237, 1921.

but the first case of idiopathic dilatation of the esophagus was described by Purton [2] in 1821, and the second by Hannay [3] in 1833. In 1841, Malrustens [4] described a case of diffuse dilatation of the esophagus without stricture, while Huss reported a similar case a year later. Rokitanski [5] and delle Chiaie [6] both reported cases in 1840, Abercrombie [7] in 1828, Oppolzer [8] in 1851, Spengler [9] in 1853 and Wilks [10] in 1859. In 1876, Zenker and von Ziemssen [11] published a study of this condition, collecting 17 cases from the literature. They emphasized the absence of stenosis and called the condition "simple ectasia." Seventeen cases were thus collected in fifty-five years, and twenty-eight years later, in 1904, von Mikulicz [12] estimated that there were 100 cases in the literature, among which were cases reported by Rumpel, Sievers, Zinnser, Rosenheim, Swain, Lockwood, Meltzer, Gregersen and Johnson. Geppert,[13] in 1914, quoted Neumann's 70 cases reported in 1900, and added 70 more.

By 1896, Wegele, Straus and Lindemann [14] had all investigated cases with various combinations of tubes, copper wires and shot. In 1908, Plummer [15] reported 40 cases from the Mayo Clinic, and in 1912,[16] 156

2. Purton, J.: An Extra Ordinary Case of Dilatation of the Esophagus, M. & Physiol. J. **46**:540, 1821.

3. Hannay, A. J.: An Extraordinary Dilatation (With Hypertrophy) of All the Thoracic Portion of the Esophagus Causing Dysphagia, Edinburgh M. & S. J. **40**:65, 1833.

4. Malrustens, quoted by Tyson, Martin and Evans.[42]

5. Rokitanski, D.: Drei merkwürdige Fälle, spindelförmige Erweiterung der Speiseröhre, Med. Jahrb. d. k. k. oesterr. Staates **21**:219, 1840.

6. delle Chiaie, S.: Istoria anatomico-teratologica intorno ad una bambina rinocefalo-monocola, Napoli, Tramater, 1840.

7. Abercrombie, John: Pathological and Practical Researches on Diseases of the Stomach, the Intestinal Canal, the Liver, and Other Viscera of the Abdomen, Edinburgh, Waugh & Innes, 1828.

8. von Oppolzer, J.: Klinische Vorträge über die Krankheiten der Speiseröhre, Wien. Med. **1**:17, 65 and 177, 1851.

9. Spengler: Beobachtungen einer Hypertrophie der Esophagus, Wien. Med. **3**:385, 1853.

10. Wilks: Lecture on Pathologic Anatomy, London, Longmans [and others], 1859.

11. Zenker, in von Ziemssen: Handbuch der speciellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1876, vol. 7, p. 1.

12. von Mikulicz, J.: Zur Pathologie und Therapie des Cardiospasmus, Deutsche med. Wchnschr. **30**:17 (Jan. 1) 1904; **30**:50 (Jan. 7) 1904.

13. Geppert, F.: Cardiospasmus und die spindelförmige Erweiterung des Oesophagus, Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **18**:149, 1914.

14. Quoted by Thieding.[1]

15. Plummer, H. S.: Cardiospasm, J. A. M. A. **51**:549 (Aug. 15) 1908.

16. Plummer, H. S.: Diffuse Dilatation of the Esophagus Without Anatomic Stenosis (Cardiospasm), J. A. M. A. **58**:2013 (June 29) 1912.

cases. In 1924, Vinson [17] stated that from 1908 to June, 1923, 415 patients had been treated in the Mayo Clinic. No other published series approaches this number.

PATHOGENESIS

It is natural that early conceptions of this disease should follow the necropsy observations. The patient who could not swallow showed at death a thin and dilated sac and no other pathologic change, so that in 1876 Zenker and von Ziemssen [11] called this condition "simple ectasia of the esophagus." In 1882, however, von Mikulicz [18] demonstrated the absence of organic stenosis by means of the esophagoscope and suggested that cardiospasm caused the dilatation. This contention was further strengthened by the study of Meltzer [19] published in 1888. It has received wide acceptance, because stretching the cardia produces a symptomatic cure. However, this has seemed inadequate to some investigators, and other theories have been suggested. Rosenheim [20] expressed the belief that the cause is a primary atony of the musculature of the esophagus. Atony of the esophagus after traumatic injury of the vagus, as well as after lead poisoning and infection, has been described by Stephan,[21] von Bergmann [22] and Meyer,[23] who pointed out the susceptibility of the vagus nerve to lead. It is a striking fact that no such dilatation of the esophagus is seen in organic stenosis. No benign or malignant stricture causes dilatation even approaching the moderate dilatation produced by cardiospasm.

Fleiner,[24] Luschka,[25] Zenker,[11] Sievers [26] and others have suggested a congenital tendency in the esophagus to idiopathic dilatation. Grein [14]

17. Vinson, P. P.: The Diagnosis and Treatment of Cardiospasm, J. A. M. A. **82**:859 (March 15) 1924.

18. von Mikulicz, J.: Ueber Gastroskopie und Oesophagoskopie, Mitth. d. Ver. d. Aerzte in Niede.-Oest. Wien **8**:41, 1882.

19. Meltzer, S. G.: Ein Fall von Dysphagie, Berl. klin. Wchnschr. **25**:140, 1888.

20. Rosenheim, T.: Beiträge zur Oesophagoskopie, Deutsche med. Wchnschr. **24**:53 and 75, 1899; Beiträge zur Kenntnis der Divertikel und Ektasien der Speiseröhre, Ztschr. f. klin. Med. **41**:177, 1900.

21. Stephan, quoted by Fisher, W., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 4, p. 101.

22. von Bergmann: Ein Fall von Dilatatio oesophagi, idiopathica, Berl. klin. Wchnschr. **45**:330 (Feb. 10) 1908.

23. Meyer, H.: Entstehung und Behandlung der Speiseröhrenerweiterungen und des Cardiospasmus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **34**:484, 1922.

24. Fleiner, W.: (*a*) Lehrbuch der Krankheiten der Verdauungsorgane, Stuttgart, Ferdinand Enke, 1896; (*b*) Neue Beiträge zur Pathologie der Speiseröhre, München. med. Wchnschr. **47**:529, 1900.

25. Luschka, V. H.: Die spindelförmige Erweiterung der Speiseröhre, Virchows Arch. f. path. Anat. **11**:429 and 473, 1868.

26. Sievers, R.: Ztschr. f. klin. Med. **49**:45, 1903.

reported a case of congenital dilatation, and noted the similarity to Hirschprung's disease. Early dilatation has been reported by Göppert,[27] Langmead,[28] Cahn,[29] Sternberg [30] and others. Congenital irregularities of the esophagus have been reported extensively (Falkenheim,[31] Stierlin,[32] Wiebrecht [33] and Zusch [34]). Guisez [35] has suggested mechanical irritation of the vagus from poorly masticated food.

Zaaijer [36] expressed the belief that the longitudinal fibers fail in the presence of paralysis of the cardia. Kraus [37] advanced the theory that besides the cardiospasm there must be paralysis of the circular fibers of the esophagus. Martin [38] felt that the dilatation was preceded by esophagitis. Kinking of the esophagus has been suggested.

The lower two thirds of the esophagus is most involved. Lockwood [39] reported a case in which there was a floating right kidney, and he suggested that reflex irritation of the vagus by this or other means may induce the cardiospasm. This possibility is strengthened by the experiments of Openchowsky,[40] and cases with this association have been reported by Smukler [41] and Tyson.[42] Ulcer and cancer of the

27. Göppert, quoted by Lotheissen, G., in Bergmann, E.; Bruns, P., and Mikulicz, J.: Handbuch der praktischen Chirurgie, ed. 4, Stuttgart, Ferdinand Enke, 1913, vol. 2.

28. Langmead, F.: Notes on a Case of Esophagectasis in an Infant, with Radiograms, Proc. Roy. Soc. Med. (Sect. Dis. Child.) **13**:43, 1920.

29. Cahn, A.: Ueber die diagnostische Verwertung der Röntgenstrahlen und den Gebrauch der Quecksilbersonde bei Speiseröhrenerkrankungen, München. med. Wchnschr. **53**:73, 1906.

30. Sternberg, W.: München. med. Wchnschr. **62**:1652, 1915.

31. Falkenheim, C.: Ein Fall von kongenitaler Cardiastenose mit diffuser Oesophagusektasia, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **33**:113, 1921.

32. Stierlin, R.: Ueber diffuse Oesophagusektasie bei wahrscheinlich angeborener Cardiastenose, Arb. a. d. Geb. d. Anat. path. Inst. zu Tübingen **7**:19, 1909.

33. Wiebrecht, K.: Ueber die Ectasien des Oesophagus, Inaug. Diss., Göttingen, W. F. Kästner, 1897.

34. Zusch, O.: Ueber spindelförmige Erweiterung der Speiseröhre im untersten Abschnitt, Deutsches Arch. f. klin. Med. **73**:208, 1902.

35. Guisez, J.: Spasm of the Esophagus, Bull. Acad. de méd., Paris **83**:147 (Feb. 17) 1920; Pathogénie et traitement des grandes dilatations de l'œsophage, Presse méd. **29**:661 (Aug. 20) 1921.

36. Zaaijer, J. H.: Cardiospasm in Aged, Ann. Surg. **77**:615 (May) 1923.

37. Kraus: Cardiospasmus, Sitzungsb. d. niederrh. Gesellsch. f. natur zu Bonn, March, 1912; Deutsche med. Wchnschr. **38**:1524, 1912.

38. Martin, E.: Zur chirurgischen Behandlung des Cardiospasmus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **8**:226, 1901.

39. Lockwood, C. B.: Brit. M. J. **1**:1367, 1903.

40. Openchowsky, T.: Ueber die gesamten Innervation der Oesophagus, Deutsche med. Wchnschr. **15**:717, 1889; **23**:48, 1897.

41. Smukler, M. E.: Cardiospasm with Dilatation of the Esophagus, New York M. J. **99**:772 (April 18) 1914.

42. Tyson, J.; Martin, E., and Evans, J. S., Jr.: Diffuse Dilatation of the Esophagus Due to Cardiospasm, New York M. J. **80**:731 (Oct. 15) 1904.

esophagus have been reported in connection with cardiospasm, and both diseases have been suggested as excitants from which reflex spasm might occur. In a case of cardiospasm associated with cancer, Loeper and Forestier [43] ascribed the cardiospasm to neurotic lesions found in the vagus and progressive and ascending canceration of the fibers in the region of the cardia. On the other hand, Palugyay [44] has suggested that spasm of the cardia may be compensatory, with pathologic changes below or in case of its own weakness.

Heyrovsky [45] reported degeneration of the vagus and its branches, the trunk showing from partial to complete degeneration. Against this are the reports of Starck,[46] Howship,[47] Rosenheim,[20] Schmidt,[48] Harbitz,[49] and others, who reported no pathologic changes at necropsy. However, Hurst [50] quoted Stokes as having found entire absence of Auerbach's plexus in 2 cases of cardiospasm sent him by Hurst. He gives Rake [51] the credit for first suggesting disease of Auerbach's plexus as a cause of this condition. Mosher and McGregor [52] confirmed the finding of Stokes of inflammation and partial or total destruction of Auerbach's plexus. They quoted Canon as having found that a pressure anemia of a given portion of the intestinal tract produced experimentally was followed in four hours by destruction of Auerbach's plexus and cessation of peristalsis. Cameron [53] reported similar findings in 7 necropsies. In 1, that of a child of 6, acute inflammation of Auerbach's plexus was found. From its character Cameron thought the

43. Loeper, M., and Forestier, J.: Recurring Cardiospasm with Cancer of the Stomach, Arch. d. mal. d. l'app. digestif **11**:307 (Oct.) 1921.

44. Palugyay, J.: Compensatory Closure of Esophagus in Dysfunction of the Cardia, Wien. klin. Wchnschr. **39**:540 (May 6) 1926.

45. Heyrovsky, H.: Casuistik und Therapie der idiopathischen Dilatation der Speiseröhre: Oesophagogastroanastomose, Arch. f. klin. Chir. **100**:703, 1912-1913.

46. Starck, H.: Zur Pathologie der Erweiterungen der Speiseröhre mit besonderer Berücksichtigung des Röntgenverfahrens, Verhandl. d. deutsch. Kong. f. inn. Med. **29**:122, 1912.

47. Howship, John: Practical Remarks on Indigestion, London, Longman [and others], 1825.

48. Schmidt, M. B.: Ueber idiopathische Oesophaguserweiterung, Deutsche med. Wchnschr. **31**:1522, 1905.

49. Harbitz, F.: Idiopatisk osophagus-dilatation, Norsk mag. f. lægevidensk. **79**:841 (Aug.) 1918.

50. Hurst, A. F.: Treatment of Achalasia of the Cardia, Lancet **1**:618 (March 19); 667 (March 26) 1927.

51. Rake, G. W.: A Case of Annular Muscular Hypertrophy of the Esophagus, Guy's Hosp. Rep. **76**:145 (April) 1926.

52. Mosher, H. P., and McGregor, G. W.: A Study of the Lower End of the Esophagus, Tr. Am. Laryng., Rhin. & Otol. Soc. **34**:294, 1928.

53. Cameron, J. A. M.: Oesophagectasia in a Child, Arch. Dis. Childhood **2**:358 (Dec.) 1927.

nervous lesion not part of an arteriosclerotic process, but "indisputable of bacterial invasion." Vampré [54] reported an epidemic of dysphagia with roentgen signs of cardia and lower esophageal spasm. Held and Gross [55] expressed the belief that cardiospasm is primarily the outcome of a hyperirritability of the vagus which may be brought about in the following 5 types of vagotonia: In the first type belong persons possessed by inheritance of unstable autonomic systems. Bed wetters, periodic vomiters and sufferers from urticaria would be the sort that make up this class. The second group would include patients with status lymphaticus with an inherent tendency to vegetative nervous instability. The third group would include all patients with reflex cases with such excitants as a floating kidney or ulcer or carcinoma of the stomach. The fourth group would include such persons as were poisoned by nicotine, uremia, gout or some other poison with a selective action on the vagus. The last group would be made up of such patients as had direct esophageal irritation, such as peptic ulcer of the esophagus, esophagitis or scar tissue formation. Mehnert [56] has pointed out abnormalities in the position of the aorta and esophagus as a causal factor.

That there is no cardiac sphincter at all has been claimed by Retzius and Cruveilhier, Fleiner,[24] Zaaijer,[36] Jackson,[57] Mosher and McGregor [52] and others.

On the other hand, Schreiber,[58] Thieding [1] and Hurst [50] expressed the belief that the usual anatomic description of a band of circular muscle fibers forming a sphincter at the lower end of the esophagus is correct.

Gubaroff [59] pointed out that the oblique entrance of the esophagus into the stomach gives a valvelike action, and Sternberg [60] expressed the opinion that the cardia is always contracted and has to be forced open. Abnormal function, then, would occur when the esophagus failed to overcome this obstruction.

---

54. Vampré, E.: Epidemic Intermittent Dysphagia, Policlinico (sez. med.) **31**:279 (May) 1924.

55. Held, I. W., and Gross, M. H.: Cardiospasm, J. A. M. A. **66**:233 (Jan. 22) 1916.

56. Mehnert, E.: Ueber die klinische Bedeutung der Oesophagus- und Aortenvariationen, Arch. f. klin. Chir. **58**:183, 1899.

57. Jackson, C.: Bronchoscopy and Esophagoscopy, Philadelphia, W. B. Saunders Company, 1927, p. 73.

58. Schreiber: Ueber den Schluckmechanismus, Berlin, 1914.

59. Gubaroff: Arch. f. Anat. u. Entwcklngsgesch., 1886, p. 395.

60. Sternberg, W.: Die Sekretentfernung bei der Oesophagoskopie, München. med. Wchnschr. **62**:468, 1915.

In 1906, Sauerbruch and Hacker [61] suggested that the diaphragmatic muscle may cause the obstruction. In 1914, Bassler [62] independently confirmed this view with five dissections and by roentgen studies. This theory has also been supported by Jackson,[63] who spoke of the diaphragmatic pinchcock constituted by the crura, and described special bundles of muscle fibers which pass from the crura to the esophagus. Jackson expressed the belief that there is no sphincter at the cardiac end of the esophagus; he said that the esophagoscope demonstrates the site of so-called cardiospasm at the hiatus, and suggested the name "phrenospasm" for cardiospasm. Joannides also takes this view, and finds that the muscle fibers of the diaphragmatic pillars bear a great resemblance to those of the anal sphincter.

Mosher and McGregor [52] noted a waistlike constriction above the level of the diaphragm and suggested that this may be caused by pressure of the tips of the lungs. Mosher [64] contended that the esophagus passes through a tunnel of liver, and that any prolapse of the liver would offer obstruction. Shortening the round ligament of the liver or suturing the liver to the diaphragm might relieve this pressure.

PREDISPOSING FACTORS

Thieding [1] expressed the belief that the person with a psychasthenic taint is predisposed to cardiospasm, and he took for granted a cortical connection with vegetative imbalance.

Imperatori [65] expressed the opinion that cardiospsm may represent the defense against fallatio fantasies. Schindler [66] regarded cardiospasm as the reaction of the patient to the necessity of keeping silent before disagreeable superiors, and he expressed the belief that psychotherapy cures the early stage. This is the answer to "children should be seen and not heard." Plummer and Vinson,[67] in a report in 1921 covering 301 cases, stated that in cardiospasm without esophageal dilatation the patients are frequently of psychoneurotic types. Concerning cardiospasm

61. Sauerbruch, F., and Hacker, R.: Zur Frage des Cardiaverschlusses der Speiseröhre, Deutsche med. Wchnschr. **32**:1263, 1906.

62. Bassler, A.: Cardiospasm: What Is It? What It Seems to Be, New York State J. Med. **14**:9 (Jan.) 1914.

63. Jackson, C.: The Diaphragmatic Pinchcock in So-Called "Cardiospasm," Laryngoscope **32**:139 (Feb.) 1922.

64. Mosher, H. P.: Liver Tunnel and Cardio-Spasm, Laryngoscope **32**:348 (May) 1922.

65. Imperatori, C. J.: Cardiospasm, Arch. Otolaryng. **11**:178 (Feb.) 1930.

66. Schindler, R.: Mechanism and Treatment of Cardiospasm, München. med. Wchnschr. **73**:1612 (Sept. 24) 1926.

67. Plummer, H. S., and Vinson, P. P.: Cardiospasm, M. Clin. North America **5**:355 (Sept.) 1921.

with dilatation they believe that, "Contrary to the general belief, cardiospasm is not a psychoneurosis, and patients suffering from it are usually calm and well balanced, with normal nervous systems." Later series, which included Plummer's cases, revealed that in 91 cases of diffuse esophageal dilatation, only 5 patients were neurotic, while in 24 cases of mild cardiospasm without esophageal dilatation, all were neurotic and some hysterical.

Straus [68] pointed out that cardiospasm occurs in an asthenic habitus. He considered it an atonic process, such as a postural defect of the stomach or the colon.

Trauma is thought to be a factor, and this is discussed by Thieding. Instances of various kinds of violence followed by cardiospasm are cited. It has been suggested that a physical shaking up can injure the ganglion cells of the vegetative plexuses, but Thieding thinks that fear in its various forms furnishes psychic trauma and produces imbalance. Sudden anger or fright may precipitate an attack, as pointed out by Fenwick.[69]

Endocrine origin of cardiospasm has been suggested. However, cardiospasm is not a feature of any of the endocrine entities.

An abnormally long esophagus has been suggested by Auerbach.[70]

No significant incidence of preceding disease has been established.

SEX AND AGE INCIDENCE

Sex.—Esophageal disease is said to be more common in males, and tobacco and alcohol are suggested as possible reasons for this. Fenwick [69] found that spasm is common in habitual drunkards, and that a debauch will precipitate an attack. Of my 13 patients, none used tobacco or alcohol to excess. Neumann [71] found 22 men to 19 women; Geppert's [13] series contained 40 men to 21 women. Albu [72] found 20 men to 2 women. But Kraus and Ridder [73] found the sexes equally affected. In my series, there were 9 women to 4 men.

68. Straus, H.: Zur Diagnose und Therapie der cardiospastichen Speiseröhrenerweiterung, Berl. klin. Wchnschr. **41**:1261 (Dec. 5) 1904.

69. Fenwick, W. S.: Spasmodic Stricture of the Cardiac Orifice of the Stomach, Brit. M. J. **1**:1126 (April 30) 1898.

70. Auerbach, B.: Diagnose und Therapie der spindelförmigen Dilatationen der Speiseröhren, Therap. d. Gegenw. **8**:150 (April) 1906.

71. Neumann, A.: Ueber die einfach gleichmässige Erweiterung der Speiseröhre, Centralbl. f. d. Grenzgeb. d. Med. u. Chir. **3**:160, 1900.

72. Albu, A.: Ein Fall von hochgradiger Esophagusdilatation, Berl. klin. Wchnschr. **45**:1109, 1908.

73. Kraus and Ridder: Die Erkrankungen der Speiseröhre, in Nothnagel: Spezielle Pathologie und Therapie, Vienna, Alfred Hölder, 1902, vol. 16, pt. 1, p. 1.

Age.—In Plummer's series, the average age of onset was 29 years. Cardiospasm may occur at any age. Cases have been reported in infants by Merv,[74] Adams,[75] La Fetra,[76] Beck,[77] Morgan,[78] Lotheissen[79] and others. Table 1 is taken from Thieding.[1]

In 13 cases, the age limit when I first saw the patients varied from 24 to 75. Three patients were 24, 26 and 27, respectively; 2 were 30 and 35; 4 were 43, 45, 48 and 48, and 1 each was 50, 58, 61 and 75. The wide age incidence is little affected by subtracting the duration of the cardiospasm from the onset to the time of admission to the hospital from the patient's age at admission. This leaves from 17 to 72 years as the age of onset, the average age being 38.

TABLE 1.—*Age Incidence of Cardiospasm*

Age	Males	Females
Up to 10 years	6	3
10 to 20	20	14
20 to 30	26	18
30 to 40	33	9
40 to 50	16	13
50 to 60	7	1
60 to 70	4	1

PATHOLOGY AND FREQUENCY

Pathology.—The dilatation may be absent early or it may be slight. Cases in which there were 2 or 3 liters have been reported.[21] Measurements of 10.5 cm. for transverse diameter, a circumference of 24 and 30 cm. and lengths of 40 and 46 cm. are quoted by Fisher.[14]

The esophagus is spindle-shaped or club-shaped, with the bowl of the club down. Less often it is sausage-shaped. The dilatation commonly can be shown to stop above the cardia at the diaphragm. The esophagus may be thickened to 9 mm., as has been shown by Starck.[46] This is mostly evidenced by hypertrophy, sometimes partly by inflammation. There is often chronic inflammation with warty, whitish thickening of the mucosa, which may be like leather. In the submucosa there is round cell infiltration. The muscularis may show fatty degenera-

74. Merv: Rev. gén. di clin. et de thérap. **22**:51, 1906.

75. Adams, S. S.: A Case of Spasmodic Stricture of the Esophagus, Arch. Pediat. **26**:170 (March) 1909.

76. La Fetra, L. E.: Spasmodic Stricture of the Esophagus, Arch. Pediat. **26**:754 (Oct.) 1909.

77. Beck, C.: Kardiospasmus im Säuglingsalter, Monatschr. f. Kinderh. **9**:555 (Oct.) 1911.

78. Morgan, W. G.: Cardiospasm in Infants, M. Rec. **80**:172 (July 22) 1911.

79. Lotheissen, G., in Bergmann, E.; Bruns, P., and Mikulicz, J.: Handbuch der praktischen Chirurgie, ed. 4, Stuttgart, Ferdinand Enke, 1913, vol. 2.

tion and infiltration. The muscle is often pigmented and may show hyaline changes. There may be atrophy of the wall in all layers. An association of congenital cleft remnants has been pointed out by Dierling.[80] Hypertrophy is likely to prevent a primary atony. If vagus disease is the cause, atony should be the common finding without hypertrophy, instead of the reverse being true. There is usually more or less chronic esophagitis.

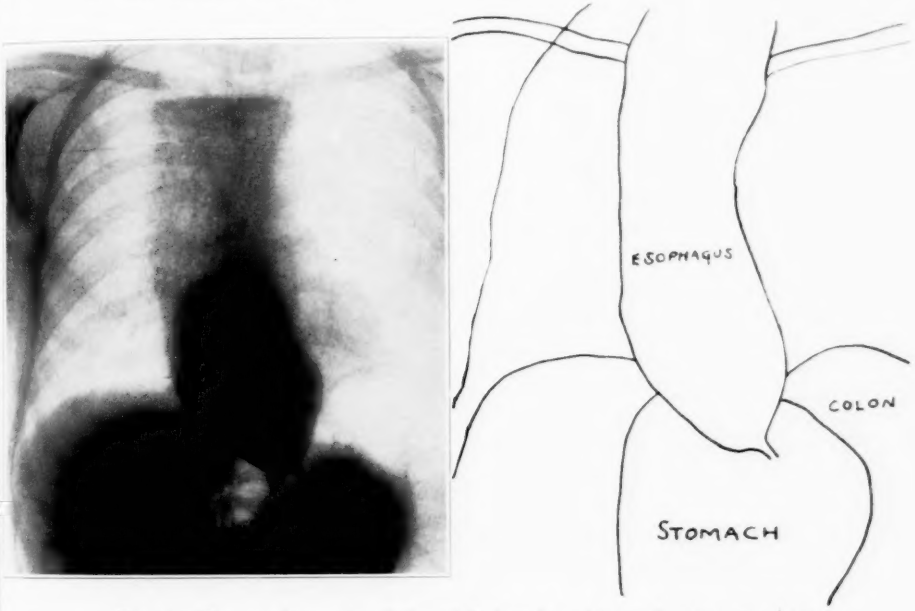


Fig. 1.—The esophagus is of the club-shaped variety and seems to show obstruction at the cardia and not at the diaphragm.

Frequency.—Thieding estimated that from 3 to 10 cases of cardiospasm are seen in any hospital in a year. There were 10 cases in Bellevue Hospital in 1930.

SYMPTOMS

The symptoms may begin suddenly, as in Tyson's case. Usually they come on gradually, with free intervals. If the onset is sudden, the patient says that while eating he had something stick in his gullet. I have twice been told that the initial symptom was caused by ham that had not been chewed sufficiently. The first attack may be severe. The

80. Dierling, H.: Ueber diffuse Dilatation der Speiseröhre, Inaug. Diss., Rostock, Adlers Erben, 1910.

patient is unable to get the offending bolus up or down. He may not be able to swallow water or even saliva. If he is able to swallow water, he may be able to force the solid food into the stomach.

Plummer divides the symptoms of cases with gradual onset, and this includes almost all cases, into three stages. These symptoms depend directly on the pathologic changes. In the first stage the cardia intermittently offers resistance to the passage of food. At all times, however, the esophagus is able to force food through. The patient then complains of discomfort, possibly pain on swallowing and sometimes of choking while eating. A common formula is: "My food seems to stick here."

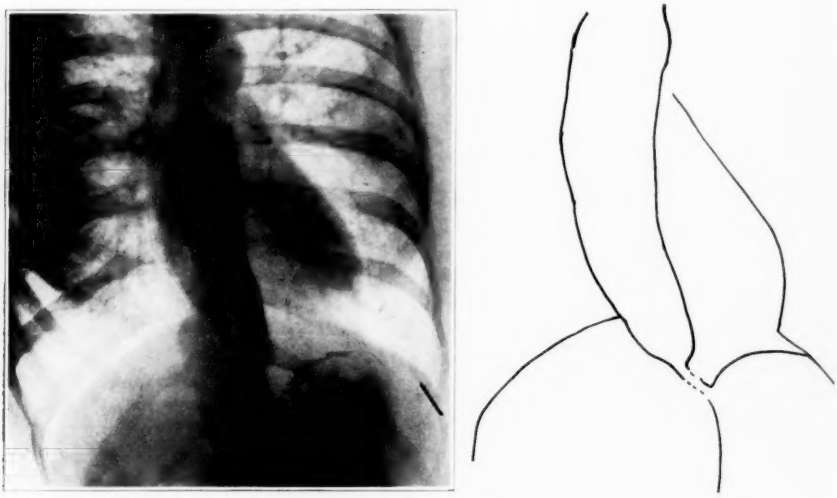


Fig. 2.—Spindle-shaped dilatation of the esophagus. The obstruction seems to be at the diaphragm.

There is no regurgitation of food in this stage. In the second stage the spasm of the cardia has become so strong that food cannot be forced through readily, and regurgitation takes place during eating. Dilatation behind the spastic cardia follows, which allows the accumulation of food in the dilated esophagus. This leads to the symptoms of the third stage, which are those of regurgitation at irregular intervals. The patient fills his esophagus to its capacity, which may be a pint or more and then may regurgitate a certain amount directly or may regurgitate at irregular intervals. In the second stage the spasm may occur with some meals and be absent with others, so that it has an irregular character, but when it does take place it is during eating. In the third stage the regurgitation is also irregular, but takes place at other times than during

actual eating, that is, just after the pouch has been filled or at varying periods afterward. These three stages shade into each other. After esophageal dilatation has taken place the food residuum gives a sensation of weight in the chest. This weight in the chest is said to be increased during anxiety, with cyanosis and cold perspiration. Verbrycke[81] has reported anginal pain with cardiospasm. Patients also complain of pain behind the whole sternum and the ramus of the lower jaw. The food regurgitated is not sour. The patient is unable actually to vomit or belch. The inability to belch is the reason for the anginal attacks, according to Fenwick. Gas gathers in the stomach until the organ is

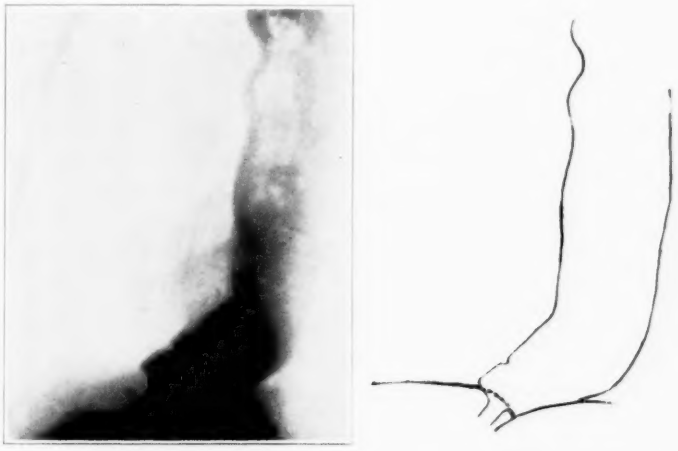


Fig. 3.—Sausage-shaped dilatation of the esophagus, showing some wavy contour above. The obstruction is at the diaphragm.

distended. Pain, sweating, palpitation and anxiety give the picture of coronary angina. My patient with transient spasm could belch and had acid eructations while asleep, which awakened him.

Rumination has been reported by Luschka.[25]

Acetone in the urine is a finding when undermaintenance of nourishment occurs.

The chief complaint is not always dysphagia, and the history may be misleading. Thus, one of my patients complained of knifelike pains over the precordium with morning vomiting; another complained that she had a peculiar pain over the epigastrium. A third said that on attempt-

81. Verbrycke, J. R., Jr.: Cardiospasm, Associated with Aneurysm, Aortitis and Angina, with Report of Twenty-Three Cases, South. M. J. **16**:338 (May) 1923.

ing deglutition she began to have a sensation in the throat as if everything tightened; it would then become so constricted that it felt like wood. This was intermittent, and three years later she began to regurgitate. Friedrich's [82] patient, a girl of 10, had attacks of coughing during which she would lie down and which were relieved by vomiting. Bard's [83] 2 patients found that they could swallow better when standing.

It is usually stated that solid foods are retained first, and the patient forces them through. This is accomplished in various ways: by swallowing saliva, by drinking liquids, by breathing, by pressure on the neck, in taking certain postures and by compression of the thorax. It becomes more and more difficult to swallow solid foods. Then soft, pultaceous foods are taken with difficulty, and finally liquids are passed more and more slowly into the stomach. Yet one of my patients with moderate dilatation of the esophagus found that the easiest foods to swallow, for her, were chop suey, corn beef hash, milk toast, macaroni and creamed vegetables. Deep breathing is thought by some to aid swallowing.

It is also said that warm liquids are more easily swallowed than cold, yet my patient who preferred chop suey could swallow ice cold water easier than warm tea or coffee.

Patients complain of vomiting, but if questioned closely or observed it will be discovered that the so-called vomiting is really regurgitation. One of my patients emptied her esophagus every morning and was all right for the day. Sometimes the regurgitation is difficult and accompanied by coughing. At other times the patients, by putting their heads low, can evacuate their gullets with comparative ease. In my case that terminated fatally the patient complained of paroxysmal pain over the upper part of the abdomen. Three attempts were made to visualize her gallbladder by the Graham method, without success. At operation the gallbladder and ducts were found to be normal. The paroxysmal pain was not explained, unless it was part of the substernal anginoid pain described. Starck [84] expressed the belief that many cases pass for gallstones, coronary angina, neurasthenia and peptic ulcer, and he saw 5 cases in which the patients were operated on for ulcer.

My 12 patients with esophageal dilatation showed no nervous symptoms. One woman, 43 years old, had an uncle who was mentally defective. She thought that the onset of her cardiospasm, thirteen years

82. Friedrich, H.: Diagnosis of Dilatation of Esophagus, München. med. Wchnschr. **71**:1278 (Sept. 12) 1924.

83. Bard, L.: Mega-Esophagus, Arch. d. mal. de l'app. digestif **10**:116 (March) 1919.

84. Starck, H.: Die Behandlung der Dilatationen und Divertikel der Speiseröhre, Deutsche med. Wchnschr. **39**:2496, 1914; München. med. Wchnschr. **71**:334, 1924.

before, was while she was very nervous. The case of intermittent spasm without dilatation occurred in a man aged 47. His mother possibly had a mild manic-depressive psychosis. He had been a sleepwalker and had a duodenal ulcer, but showed no other neurotic taint.

Rivers and Bueermann [85] reported 3 cases in which attacks of unconsciousness were associated with intermittent cardiospasm, one being a very definite case. They called these attacks, which were short, "epileptiform," and compared them to laryngeal epilepsy. The patient suddenly becomes unconscious while eating. He recovers immediately and goes on eating.

PHYSICAL SIGNS

Various physical signs have been described. Dulness to the right of the sternum, below which it changes to tympany when the esophagus is full of air, moist râles when air is pumped in and absence of the second swallowing sound have been described. Bradycardia was described by Heyrovsky,[45] Kaufmann and Kienböck [86] and Schulze.[87] It did not occur in my series.

Hyperacidity is often found in the stomach, but 1 of Soper's [88] patients had achlorhydria. Hyperacidity would be the thing to expect with vagus preponderance, but Thieding pointed out that a vegetative disharmony is rarely pure, and that mixed sympatheticotonia and vagotonia are described by Eppinger and Hess.

ASSOCIATED DISEASES

The association of diverticulum of the esophagus with cardiospasm has been mentioned by Zohlen and Vinson,[89] Fitzgibbon,[90] Bull,[91] Dufour,[92] Van den Wildenberg,[93] Freud [94] and others.

85. Rivers, A. B., and Bueermann, W. H.: Recurring Epileptiform Attacks with Symptoms of Spasm at Cardia, M. Clin. North America **8**:1341 (Jan.) 1925.

86. Kaufmann, R., and Kienböck, R.: Ueber Erkrankungen der Speiseröhre, Wien. klin. Wchnschr. **22**:1199, 1909.

87. Schulze, J.: Röntgenologische Beobachtungen über funktionelle Vërhaltnisse der Speiseröhre, München. med. Wchnschr. **64**:879, 1917.

88. Soper, H. W., and Cassidy, L. D.: Cardiospasm with Special Reference to Etiology, Am. J. M. Sc. **177**:386 (March) 1929.

89. Vinson, P. P.: Cardiospasm Associated with Esophageal Diverticula, New York M. J. **117**:540 (May 2) 1923.

90. Fitzgibbon, J. H.: Cardiospasm and Concomitant Esophageal Diverticulum, J. A. M. A. **86**:1614 (May 22) 1926.

91. Bull, P. N.: So-Called Idiopathic Dilatation of the Oesophagus, Ann. Surg. **81**:59 (Jan.) 1925.

92. Dufour, H.: Bull. et mém. Soc. méd. d. hôp. de Paris **19**:1057, 1902.

93. Van den Wildenberg, L.: Quelques cas de méga-œsophage, Ann. de mal. de l'oreille, du larynx **43**:945, 1924.

94. Freud, J.: Zur Röntgendiagnose des seltenen tiefsitzenden Oesophagusdivertikels, Fortschr. a. d. Geb. d. Röntgenstrahlen **28**:559, 1921.

Asthma is said to be frequently associated with cardiospasm by Scollery, von Bergmann [95] and Lindvall.[96]

Other spastic conditions have also been mentioned. Zinn [97] found esophageal spasm behind the heart. Thieding found spasm behind the bifurcation. I have had a patient with spasm behind the larynx.

The association with peptic ulcer is common. Heyrovsky, quoted by Soper and Cassidy,[88] reported 6 cases connected with gastric ulcer, and found 7 cases of ulcer in a series of 29. In this connection, the experiments of Gundelfinger [98] relative to a neurogenous vagus preponderance influencing the formation of ulcer is interesting. The autonomic origin of ulcer is discussed by von Bergmann,[95] Kaufmann,[99] Müller [100] and Kuntz,[101] among others, and Westphalen [102] has pointed out that disease of the autonomous centers can cause an independent organic neurosis of the cardia and the stomach which may be due to disharmony of the plexus of Openchowsky and that of Auerbach.

Carcinoma of the stomach and esophagus is found in significant association. It was present 3 times in Soper's [88] series of 29 cases. Thieding found that it is a complication 25 times more likely than in the normal esophagus. Albu,[72] Bensuade and Guénaux,[103] Guisez,[35] Fleiner,[24b] Grund,[104] Knaut,[105] and many others have reported cancer and cardiospasm. De Anciaes [106] reported the association of sarcoma.

Gallstones are also mentioned in association.

---

95. von Bergmann, G. V.: Das Spasmogene Ulcus pepticum, München. med. Wchnschr. **60**:169, 1913.

96. Lindvall, H.: Case of Diffuse Dilatation of the Esophagus Combined with Bronchial Asthma, Hygiea **77**:860, 1915; Zentralbl. f. Chir. **43**:99 (Feb. 5) 1916.

97. Zinn: Gleichmässige Erweiterung der Speiseröhre, Berl. klin. Wchnschr. **47**:1515 (Aug. 8) 1910.

98. Gundelfinger, E.: Klinische und experimentelle Untersuchungen über den Einfluss des Nervensystems bei der Entstehung des runden Magengeschwürs, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **30**:189 and 229, 1918.

99. Kaufmann, R.: Ueber den Einfluss des Schmerzes und der Digitalis auf die Herzarbeit des normalen Menschen, Ztschr. f. exper. Path. u. Therap. **12**:165, 1913.

100. Müller, E. F.: Ueber eine gemeinsame Steuerung von Haut und Lebergebiet, München. med. Wchnschr. **73**:9 (Jan. 1) 1926.

101. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929.

102. Westphalen, H.: Ein weiterer Fall von diffuser idiopathische Oesophagusdilatation, Arch. f. Verdauungskr. **5**:106, 1899.

103. Bensaude, E., and Guénaux, G.: Rev. de méd. **38**:65 (Feb.) 1921.

104. Grund, in discussion of Beneke: Ueber Oesophagusdilatationen, München. med. Wchnschr. **61**:1882, 1914.

105. Knaut, B.: Ueber die durch Speiseröhrenkrebs bedingten Perforationen der benachbarten Blutbahnen, nebst einer Beobachtung von primärer Oesophagusdilatation und von Leukoplakia œsophagi, Inaug. Diss., Berlin, Vogt, 1896.

106. de Anciaes, C.: Idiopathic Dilatation of the Esophagus, Lisboa méd. **2**:415 (Sept.) 1925.

No associated disease of any significance was found in my series. None of the patients had a positive Wassermann reaction, although one woman had 6 miscarriages in 9 pregnancies, and another had 1 stillbirth in 5 pregnancies; a third had 1 miscarriage and 1 healthy child. The first of these patients had had measles, chicken-pox, pertussis, pneumonia and scarlet fever. The second patient had had rheumatic fever and pneumonia. The third had had influenza. Of the remainder, 1 woman, 30 years old, married but never pregnant, had had measles and mumps. A 75 year old man with cardiospasm of two years' duration had used alcohol in moderation; he gave a history of "blood poisoning" two years before and gonorrhea forty years before. No other history of disease was obtained. The woman, aged 43, who had 6 miscarriages, had had a complete hysterectomy three years before she was seen. Her cardiospasm was of thirteen years' duration. The 75 year old man had had a cyst on his right eye removed six years before.

DIAGNOSIS

Various methods of diagnosis have been suggested and used. Before roentgen study was possible, the usual methods were several. Auscultation for the second swallowing sound, which is absent in cardiospasm, was recommended. A device of Meltzer and Rumpel was the double tube test, which consisted in passing a tube into the stomach and another along the side into the esophageal pouch. The acid secretion of the stomach differed from the esophageal contents, so that matter aspirated from the two cavities gave a different appearance and response to tests. In the esophageal contents there are almost always great quantities of thick ropy mucus. The size of the dilatation was measured by filling the pouch with water and aspirating.

Esophagoscopy.—This method of examination is, in proper hands, the ideal method for diagnosis in most diseases of the esophagus. It is perhaps less valuable in mega-esophagus than in any other condition. Unfortunately it is a hazardous procedure in any but skilled hands and should not be attempted by the novice without instruction and supervision. Jackson [57] emphasized that injury to the crico-arytenoid joint, paralysis due to pressure on the recurrent laryngeal nerve, perforation of the esophageal wall and rupture of an aneurysm are possibilities without gentleness, care and experience; he also warned against attempting esophagoscopy in patients with tuberculosis, heart failure or some other advanced organic disease. I have seen 1 death during esophagoscopy without apparent reason. In cases of cardiospasm, esophagoscopy is largely valuable in excluding other diseases, particularly cancer.

Roentgen Study.—This is the accurate method of demonstrating cardiospasm, and by this method diagnosis can be made and complications excluded. Cardiospasm diagnosed during life was a great rarity before roentgen study was possible. Up to 1904, 100 cases were reported. During 1930, there were 20 cases diagnosed in the Department of Hospitals of the City of New York. Carman [107] gave the roentgenologic characteristics as blunt or regularly conical obstruction at or near the cardia, with secondary dilatation of the esophagus above. The smooth symmetrical termination of the shadow is a feature and usually comes at the hiatus and less often at the cardia. Dilatation may reach a point where the contents are a pint or more. Cardiospasm must be differentiated from benign organic stricture and from carcinoma. In differentiation from the latter, it is useful to know that carcinoma rarely produces its obstruction at exactly the hiatus, but usually extends above. In carcinoma there is irregularity of the shadow as it tails out. Benign stricture is usually irregular also, though sometimes a differential diagnosis is difficult.

The esophagus is seen best in the oblique, either in the right fencing position of Holzknecht or in the left oblique, and Stierlin [108] suggested the advantage of profile views. In cardiospasm one notes at once the contrast meal retained in the esophagus, with or without a demonstrable small stream trickling into the stomach. The striking thing is the size of the esophagus, which may be large. The lower end is cone-shaped, and the tip points to the left below the dome of the diaphragm. The length of the esophagus may be increased, so that it presents a wavy appearance. It may be cylindric and of uniform width, it may be spindle-shaped, with the dilatation in the center, or it may have a champagne bottle shape.[1] In 1914, Lambert [109] described the 3 contours as fusiform, flask-shaped and S-shaped. Fleiner [24b] has called attention to the hen beak appearance of the shadow that projects into the stomach, which he thinks is due to the gastric pathway. Hirsch [110] expressed the belief that this is due to the stream passing into the longitudinal rugae. Einhorn and Scholz [111] have made use of a delineator string which is swallowed and gives the esophageal course.

---

107. Carman, R. D.: The Roentgen Diagnosis of Diseases of the Alimentary Canal, Philadelphia, W. B. Saunders Company, 1921.

108. Stierlin, R.: Klinische Röntgendiagnostik des Verdauungskanals, Munich, J. F. Bergmann, 1916.

109. Lambert, A. V. S.: Treatment of Diffuse Dilation of the Oesophagus by Operation: Report of a Case, Surg., Gynec. & Obst. **18**:1, 1914.

110. Hirsch, A.: Ueber diffuse Dilatation des Oesophagus durch Cardiospasmus, München. med. Wchnschr. **40**:1149, 1919.

111. Einhorn, Moses, and Scholz, T.: X-Ray Findings with the Delineator in Cardiospasm, Med. Rec. **96**:715, 1919.

Iglauer [112] recommended the use of pneumoperitoneum in the roentgen study of cardiospasm. In one case, he found that this showed adhesions between the diaphragm and the liver, encroaching on the abdominal esophagus.

COMPLICATIONS

The complications of cardiospasm which are dependent on it are rupture of the cardiospasm with mediastinitis, either spontaneous or by bougie; ulcer of the esophagus or stomach, which must be considered in mechanical treatment, and carcinoma of the esophagus. Thomas and Jewett [113] reported a case of pneumonia following aspiration of fats from a dilated esophagus due to cardiospasm.

PROGNOSIS

When treated by mechanical dilatation, the patients recover. Treatment is easier the earlier it is done. There is some mortality with the

TABLE 2.—*Duration of Cardiospasm*

Duration	Cases
1 year or less	23
Less than 5 years, over 1	59
Less than 10 years, over 5	33
Less than 15 years, over 10	17
Less than 20 years, over 15	9
Less than 30 years, over 20	7
Over 30 years	1

procedure. Perforation of a paper thin esophagus is possible. It is fortunate that hypertrophy is the rule. Rupture of the cardia or injury to an ulcer just above, in or below the cardia may result in hemorrhage or perforation. So, as a matter of prognosis, the accidents of treatment constitute the chief hazard, although Zweig [114] reported a case of Wicks', with fatal hemorrhage from an ulcer in the dilated portion.

Untreated patients may live for years on a diet so modified that enough food gets into the stomach to support life. The obstruction may reach such a degree as to cause death by starvation.

The duration of cardiospasm from the beginning to the time of observation is given by Thieding in table 2.

112. Iglauer, S.: Pneumoperitoneum as an Aid in the Diagnosis of Cardiospasm, New York M. J. **115**:745 (June 21) 1922.

113. Thomas, W. S., and Jewett, C. H.: Pneumonia Following the Aspiration of Fats from the Esophagus Dilated as a Result of Cardiospasm, Clifton M. Bull. **12**:130 (Dec.) 1926.

114. Zweig, W.: Ueber Kardiospasmus, Wien. klin. Wchnschr. **22**:740, 1909.

My 13 cases were of ten months, one, two, three, three, three, five, five, six, six, seven, ten and thirteen years' duration. Snodgrass [115] reported a case of fifty-two years' duration.

TREATMENT

Medical treatment with atropine has proved disappointing. Papaverine has been used and was believed by Thieding to cure one of his patients. However, Boehm [116] found no benefit from papaverine, and Assmann found no effect with this drug in 3 cases. Boehm found that after the administration of pilocarpine there was shortening of the esophagus with overflow. Epinephrine relaxed the cardia, but the effect was transitory. No other drugs produced favorable therapeutic results.

In 1900, von Mikulicz [12] performed gastrostomy on a girl to dilate the cardia. Three years later he opened the stomach of another subject and, having stretched the cardia with 3 fingers, he introduced a rubber-covered dilator and further stretched the cardia to a circumference of 13 cm. He performed this operation 6 times with good results. Ledderhose [14] in 1904, Wilms [14] in 1904 and Goldmann [14] in 1905 reported single operations. In 1906, Erdmann,[117] of New York, operated on a patient of Lockwood's, with recovery. In 1910, Wendel [118] performed the first cardioplasty. Watts [119] expressed the belief that cardiospasm is likely to recur after dilatation and after the Mikulicz operation. He had a patient who was only temporarily improved by the Mikulicz operation on whom he did what he believed was the second cardioplasty after the manner of Wendel. Heller [120] made two longitudinal incisions, one anterior and one posterior. In the Wendel and Watts operations, one incision only was made, the longitudinal. The beginnings and ends of the incisions were then approximated, the sides were thus bent on themselves and the upper half was sutured to the lower half. De Bruine, Groeneveldt and Zaaijer [36] reported success with a single anterior incision. Heyrovsky [45] loosened the cardia at the hiatus and anastomosed the esophagus and stomach. Häggström [121] collected 29

115. Snodgrass, T. J.: Case of Cardiospasm with Enormous Dilatation of the Esophagus, J. Iowa M. Soc. **11**:212 (June) 1921.

116. Boehm, G.: Der Cardiospasmus mit Ektasie der Speiseröhre und seine Behandlung, Deutsches Arch. f. klin. Med. **136**:358 (July 5) 1921.

117. Erdmann, J. F.: Cardio-Spasm, Ann. Surg. **43**:224 (Feb.) 1906.

118. Wendel: Zur Chirurgie des Oesophagus, Arch. f. klin. Chir. **93**:311, 1910.

119. Watts, S. H.: Cardioplasty for Cardiospasm, Ann. Surg. **78**:164 (Aug.) 1923.

120. Heller: Extramuköse Cardiaplastik beim chronischen Cardiospasmus mit Dilatation des Oesophagus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **27**:141, 1914.

121. Häggström, P.: Heyrovsky's Operation for Cardiospasm and Dilatation of the Esophagus, Acta chir. Scandinav. **66**:345, 1930.

cases in which Heyrovsky's operation was performed by the transperitoneal route. These, he stated, were all successful, whereas 2 of every 5 patients die when the transpleural route advocated by Sauerbruch [122] is used.

Freeman [123] pulled up the esophagus and, turning the slack portion in, made an intussusception, with apparent cure twenty years later. Pamperl collected the cases of 14 patients operated on by the Mikulicz method, with 12 cured and 2 improved. Walton has operated on 14 patients with satisfactory results. Crone-Münzebrock,[124] Greenwood and others have also endorsed this treatment.

Following the success of the Mikulicz operation, various efforts were made to dilate the cardia by expanding instruments introduced into the cardia through the mouth. If such an instrument could be devised, it seemed reasonable that abdominal section could be done away with except in unusual and infrequent cases.

Rosenheim,[20] Lockwood,[39] Einhorn,[125] Gottstein [126] and others devised instruments for this purpose. Gottstein's sound is generally given priority in the German literature, but it was in 1898 that Russell [127] reported that in a radius of less than 40 miles from Southport, England, he had seen 7 cases of a form of stricture of the esophagus which he believed could not be extremely rare. Russell reported good results from stretching the stricture by an expanding dilator to a caliber approaching that of the normal esophagus. This was done with bags of increasing size at several sittings. He made sausage-shaped silk bags which were made air tight by a thin rubber bag within and mounted on the end of a hollow tube. This was passed through the stricture collapsed, and was blown up with an air syringe when in position. By gradual dilatation, Russell cured 4 of 6 patients and improved another very much. The seventh patient he did not treat.

122. Sauerbruch, F.: Oesophagusstriktur; Cardiospasmus, Verhandl. d. deutsch. Gesellsch. f. Chir. **45**:149, 1921.

123. Freeman, L.: Operation for Relief of Cardiospasm Associated with Dilatation and Tortuosity of Œsophagus, Ann. Surg. **78**:173 (Aug.) 1923.

124. Crone-Münzebrock, E.: Operative Treatment of True Cardiospasm, Zentralbl. f. Chir. **53**:2386 (Sept. 18) 1926.

125. Einhorn, Max: Report of a Case of Idiopathic Dilatation of the Esophagus with Description of a New Cardio Dilator, New York M. J. **89**:1077 (May 29) 1909; Additional Remarks on Cardiospasm and Idiopathic Dilatation of the Esophagus, M. Rec. **83**:369, 1913.

126. Gottstein, G.: Die operative Behandlung Cardiospasmus, Zentralbl. f. Chir. **31**:1362 (Nov. 26) 1904; Weitere Fortschritte in der Therapie des chronischen Cardiospasmus, Arch. f. klin. Chir. **27**:497, 1908.

127. Russell, J. C.: Diagnosis and Treatment of Spasmodic Stricture of the Œsophagus, Brit. M. J. **1**:1450 (June 4) 1898.

One patient he did not help. Sippy [128] was able to confirm these results in 1906. Plummer [129] made use of a similar method, employing water instead of air to dilate the rubber bag. In 1908, he had treated 40 patients by this method. This number he had increased to 156 by 1912, and in 1923 Vinson had increased this series to 415.

Ordinary bougie treatment may help symptoms partially and temporarily, but dilatation must be carried further for permanent and striking results. Oehler [130] reported good results from passing the stomach tube. He teaches his patients to pass it, and when passage is effected without discomfort, the patient is usually cured.

Several different forms of dilating instruments are in use. The simplest of these consists of an ordinary stomach tube fenestrated at one end. Over these fenestrations is drawn a rubber tube or bag. This is secured above and below the openings. Over this is a silk bag to limit the distention of the rubber, and this in turn is covered with another layer of rubber. The last two layers are secured about the stomach tube as was the first by tying with silk. This may then be connected with a water tap, and the water running through the stomach tube and out the fenestrations distends the rubber bag, guarded by the silk bag, according to the force of the stream allowed to run in. If the end of the stomach tube covered with the rubber bags is passed into the cardia while collapsed and the water is turned on, as the water distends the bag the cardia will be dilated. This gives the patient considerable pain, and it may be a guide to the amount of distention and to the length of time dilatation is continued. Plummer believes that pain is not a reliable symptom, and that the pressure should be measured. Insertion of such a large contrivance may be difficult or impossible, so that preliminary dilatation with bougies is required.

It is difficult to enter the cardia with even small bougies in some cases, and the string method used in dilatation of esophageal stricture is used. The patient swallows an end of silk ligature. Number 6 does very well. A lead shot may be fixed on the end to facilitate swallowing. The patient keeps on swallowing until 5 or 6 yards have been swallowed. Then small metal olives on a flexible rod, the silk thread running through a hole entering the tip of the olive and passing out of the back, are pushed down the esophagus, and, guided by the silk ligature, are passed into the stomach. These olives are gradually increased in size. When one of sufficient size has been passed, a dilating

128. Sippy, B. W.: Paper read at a meeting of the American Medical Association, 1906; not published; quoted by Plummer.[15]

129. Plummer (footnotes 15 and 16).

130. Oehler, J.: Treatment of Cardiospasm, München. med. Wchnschr. **69:** 1482 (Oct. 20) 1922.

bag is next used, which has a perforated olive at its tip. This is guided into the stomach in the same manner that the olives on the flexible rod were passed. With the bag in place, hydrostatic dilatation is possible.

Plummer has made use of a gage to record the water pressure that is being used. The pressure is expressed in terms of feet of water. Myers does not use a gage, but is guided by the pain experienced by the patient. Plummer's dilator is made up as follows: A stomach tube about 30 French is used. This is open at both ends. The end that is to be passed into the esophagus tapers slightly, and into this is fastened a piece of hollow metal tube about 3 cm. long. This tubing has two indentations on the outside, one to permit fastening the stomach tube and one to permit fastening the rubber and silk bags. The end designed to project beyond the stomach tube has a screw thread, and onto this the perforated olive screws. A rather stiff woven silk stylet attaches to the metal tube inside the stomach tube, small enough not to interfere with the passage of water down the tube. This stylet is shorter than the stomach tube, but is long enough so that it can be grasped through the tube and used, thus giving rigidity to the tube and making its passage easier. To provide the water pressure a rubber tube is connected to the water tap. Objection to the Plummer dilator is that its stylet allows the operator to push the instrument into place regardless of minor obstruction. I have had 1 fatality from a perforated esophagus with this instrument which would not have occurred with a Lerch dilator, which consists of a rubber tube and bag without metal or a stylet on the end. When one attempts to push the rubber stomach tube it is not stiff enough to perforate the esophagus, but works its way along. On the other hand, it is impossible to force the Lerch instrument into some stomachs in which one might be successful with the Plummer instrument.

From 2 to 5 dilatations are made. Many patients are relieved by a pressure equal to a column of from 16 to 22 feet of water. In marked cases from 24 to 28 may be given. If a fissure or ulcer is present, one should dilate a little and then wait. The patient is cured if the esophagus functions normally ten days after any dilatation. About 25 per cent require a second stretching later. Vinson's mortality is 1 in 350 cases. Whatever method is used, it is a hospital procedure.

Straus [68] has also passed a spindle-shaped bag collapsed. It is then blown up and withdrawn. This was reported six years after the similar method of Russell. Starck [84] has an expanding dilator which he passes through the esophagoscopy under direct vision. Maydl [131] used this

131. Maydl, V.: Treatment of Cardiospasm with Starch's Sound, Casop. lék. česk. **67**:877, 1925; abstr., J. A. M. A. **85**:480 (Aug. 8) 1925.

method with success in 5 cases. Hurst [59] constructed mercury bougies. These are rubber tubes varying in diameter from thirty-three sixty-fourths to forty-six sixty-fourths inch and are each 31 inches long. Each bougie contains 1 pound and 5 ounces (595.3 Gm.) of mercury. He has had but one case in which he could not pass the tubes. Lyon [132] treated a patient with bougies of increasing size, and followed this by a galvanic current and then a sinusoidal current.

It seems inevitable that an instrument will be devised less cumbersome and awkward than the hydrostatic dilator and with which the pressure can be more easily controlled. Possibly such an instrument has been devised by Zohlen.[133] I have had no experience with the Zohlen dilator, but it seems to be promising.

SUMMARY

An account of cardiospasm with dilatation of the esophagus is given, recounting the history, pathogenesis, contributing factors, pathologic changes, age, duration, sex, symptoms, esophagoscopy, roentgen study, complications, associated diseases, diagnosis, prognosis and treatment. A review of the literature and data from 13 personally observed cases are given.

---

132. Lyon, B. B. V.: A Consideration of Cardiospasm with Report of a Case, Am. J. M. Sc. **151**:389 (March) 1916.

133. Zohlen, J. P.: A New Collapsible Esophageal and Cardiospasm Dilator, Wisconsin M. J. **28**:168 (April) 1929.

MODE OF PRODUCTION OF THE FIRST HEART SOUND

WILLIAM DOCK, M.D.
SAN FRANCISCO

The experimental observations on dogs' heart sounds here described were intended to cast further light on the relative importance of muscular and of valvular elements in the production of the first heart sound. The theory based on these observations seemed to conflict with the views of recent workers, particularly with those of Wolferth and Margolies in their excellent study of the variations of intensity of the first sound in heart block. The relation between auricular systole and the first sound is therefore described in some detail. It is believed that the theory offered gives a coherent explanation of all the phenomena noted in the study of the first heart sound.[1]

METHODS

Dogs anesthetized with a brand of chlorbutanol were subjected to midline thoracotomy, and respiration was artificially maintained. The heart sounds were recorded by a collodion Frank capsule from small tambours attached to the ventricular surface by short rigid levers. This is a modification of the method of Wiggers and Dean.[1a] The vibrations recorded resemble in form and amplitude those obtained with Frank capsules in the clinical study of heart sounds. Electrocardiograms were recorded from copper wire leads inserted in the shoulder and thigh muscles, through a 20 microfarad capacitance in series with the string galvanometer. Digifolin, injected directly into the ventricle, was used to produce ventricular tachycardia and fibrillation. Isometric ventricular contractions were obtained by putting a heavy cord, covered with petrolatum, around the atrioventricular groove and suddenly drawing it tight so as to prevent blood from entering or leaving the ventricles. When the ligature around the auriculoventricular ring

From the Department of Medicine, Stanford University School of Medicine.

1. Historical Note: The theory supported by the discussion in this paper was first stated, without adequate experimental evidence, by J. Rouanet, in a thesis, Analyse des bruits du coeur, given in Paris on Aug. 31, 1832. The following is my translation of some statements from page 8: "The shock of blood against the valves, or of valves against the heart wall, the shock which might result from two bodies colliding, is not the only cause of a valvular sound. From many experiments I have learned that any membrane, passing from flaccidity to tension suddenly, always make a sound. . . . The auriculoventricular valves present conditions which are most favorable for the production of sound; they are thin and tough, and do not stretch; they pass instantly from the most complete flaccidity to sudden and violent tension."

1a. Wiggers, C. J., and Dean, A. S., Jr.: The Nature and Time Relations of the Fundamental Heart Sounds, Am. J. Physiol. **42**:476, 1917.

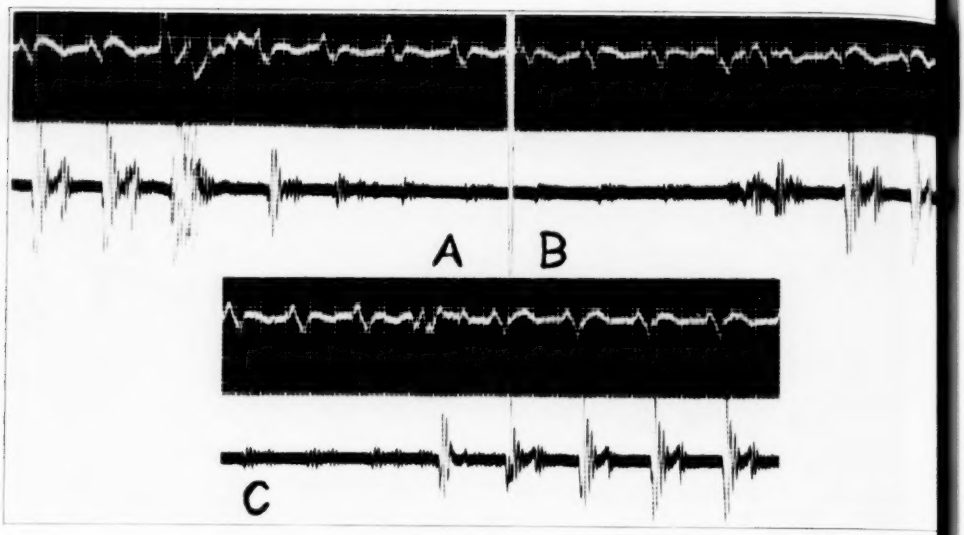


Fig. 1.—*A*, the effect of clamping off the venous flow to the heart; *B* and *C*, the effect of releasing venous inflow (dog 6).

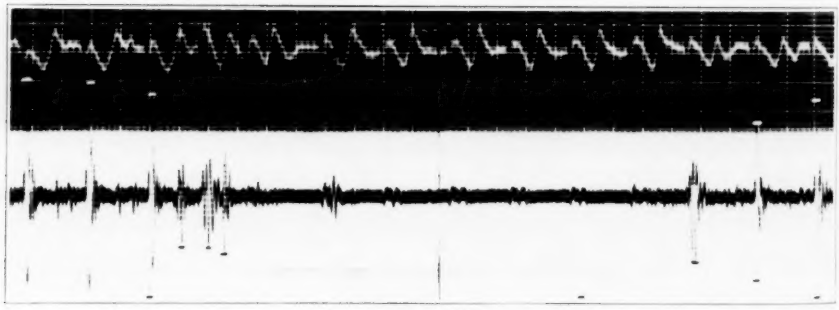


Fig. 2.—The effect of closing and opening the clamp on the venous inflow of the dog's heart on the intensity of the heart sounds (dog 9).

was tightened, the heart was sometimes caught full of blood; at other times, at the end of systole, it was small but still much larger than when venous filling was prevented. Tightening this ligature produced, in one instance, a high degree of auriculoventricular heart block. A rubber-faced, spring-bladed enterostomy clamp was used to close the openings of the great veins into the auricles. One blade was passed between the auricles and the pulmonary artery and aorta; the other was brought behind the apex of the heart, and the clamp, nearly closed but permitting normal circulation, was left in place behind the auricles. By opening and closing the clamp, venous filling could be started or stopped at will. When the clamp was closed, the heart became small and bloodless, but contracted vigorously.

Sum of the Amplitudes of the Three Largest Vibrations of the First Heart Sound Records, in Different Dogs and Under Various Conditions of Cardiac Activity

	Ventricular Tachycardia, Mm.	Rapid Ventricular Fibrillation, Mm.	Slow Ventricular Fibrillation, Mm.
Dog 5	43	0	0
	Venous Inflow Normal	Venous Inflow Shut Off	Venous Inflow Released
Dog 4	31	2.5	25
Dog 6	40	2.5	37
Dog 7	34	1.5	34
	42	1.5	34
	37	1.5	36
Dog 9	52	1.5	37
	63	4.0	53
	38	2.0	47
	34	1.5	36
Dog 10	23	1.0	26
	22	1.0	30
	22	1.0	19
Dog 11	31	2.5	34
Average	36	1.8	34.5
	Normal Flow	Ligature Around Auriculo-ventricular Groove	
Dog 10	31	0.5	
Dog 11	25	3.5	
Average	28	2.0	

RESULTS

During ventricular tachycardia the first sound was loud, but with the onset of fibrillation all sounds ceased. Violent incoordinate muscular activity was visible; the muscle was under some tension and the heart maximally dilated, but such muscular activity produced no sounds comparable to those audible with normal heart action (table).

When the heart beat isometrically the sound production either ceased entirely or was greatly diminished (table). When the heart was empty, because of impaired venous return, the heart sounds entirely ceased, but some vibration due to the violent mechanical movement of the receiving tambour remained (figs. 1 and 2). As seen in the table,

clamping off the venous inflow, in thirteen attempts on five dogs, gave an average reduction of 95 per cent in the amplitude of vibrations produced in early systole, while the ligature around the auriculoventricular ring reduced the amplitude by 93 per cent. Not only was the amplitude diminished, but the recorded vibrations were so different in form from those recorded from the hearts before circulatory conditions were altered as to leave no doubt that in clamped-off or ligatured hearts the recorded vibrations were inaudible mechanical effects of ventricular movement.

COMMENT

Extensive discussions and bibliographies on the theories and experimental observations on the first heart sound have been given recently by Schutz [2] and by Frey.[3] Five theories, with variations, have been advanced in explanation of these vibrations. Briefly, the sound is supposed to originate in the closure of the auriculoventricular valves, in the friction of contracting ventricular muscle, in the change in tension in the aorta and pulmonary artery, in the change in tension in the coronary vessels (Laurell,[4] 1931) and finally, according to the thesis accepted by both Schutz and Frey, in the physical changes in tension of the ventricles during the rise of intraventricular pressure. The customary explanation given in recent texts on heart disease and on physical diagnosis is that the first sound is both muscular and valvular in origin, but it is not stated how the muscle or valves set up audible vibrations. No theory has been elaborated to account for the accentuated heart sound heard in some cycles in cases of complete heart block or in cases of mitral stenosis.[5]

2. Schutz, E.: Experimentelle Untersuchungen über die Entstehung der Herztone, Ztschr. f. d. ges. exper. Med. **77**:348, 1931.

3. Frey, W.: Die Ursachen der Entstehung der Herztone, in Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1926, vol. 7, pt. 1, p. 292.

4. Laurell, H.: Die Coronarkreislauf ein übersehener Faktor bei der Deutung der Druck- und Schallphänomene im Herzen, Upsala läkaref. förh. **36**:133, 1931.

5. Historical Note: In 1841 James Hope (London M. Gaz. **30**:310, 1841) wrote of his previous experimental work, described in an appendix to the second (1835) edition of his "Treatise": "The first sound was shown by evidence verging upon demonstration to be occasioned partly by sudden extension of auricular valves and chordae tendineae, and partly by similar violent extension of the muscular walls at the moment the valves close." This is the earliest statement of the theory now held in Germany. In 1851, G. B. Halford (Lancet **2**:593, 1851) first performed the experiment which demonstrated the absence of a muscular element in the first heart sound, with a technic not unlike that used in the experiments of this paper. Halford wrote: "The superior and inferior vena cava and the pulmonary veins at the entrance to the left auricle were tightly compressed between the fingers. The heart continuing its action, a stethoscope was again applied, and neither first nor second sound was heard." Halford's crucial experiment is not referred to by subsequent investigators, although others observed similar phenomena.

From the experimental evidence, summarized in the papers just mentioned, it is quite clear that the contraction of ventricular muscle does not, in the intact heart, produce an audible vibration, although, according to unpublished work of Wiggers and Dean,[6] vibrations can be recorded from strips of cat ventricle. The experiments reported in this paper demonstrate that vigorous ventricular systole may produce no sound. Sound production in the root of the aorta or in the coronary vessels may occur, but since the main vibrations of the first sound occur before the pressure changes in these vessels it is unlikely that they contribute any important element. The theory accepted by Schutz and Frey, namely, that the sudden change in tension of the structures in the ventricular walls causes audible vibrations, includes the auriculoventricular valves as part of the vibrating mass. As given by Schutz, this theory is stated thus:

> With the suddenly developing contractile process of the myocardium, the active tensing of the elastic heart-wall around its incompressible content releases vibrations of audible frequency (and intensity). These vibrations can be experimentally demonstrated in relation to the first heart sound, both on the ventricular walls and in the curves of intra-auricular pressure near the auriculoventricular valves.

This theory, as given by Schutz, Frey and others, ignores the accentuation of the first sound in mitral stenosis and in the ventricular beats, in cases of heart block, which occur shortly after auricular beats. However, some such explanation seems to be accepted by Wolferth and Margolies[7] to account for these clinical phenomena. The validity of such an explanation will be considered shortly, but it is obvious that, according to this theory, sound production should be quite normal in the isometrically contracting heart if the ventricular cavities are filled. The experiments on the dogs whose ventricles were tied off by a ligature in the auriculoventricular groove show that sound is not necessarily produced by the "tensing of the heart-wall around its incompressible content." Experimental findings, so at variance with theory, seem to justify the rejection of the theory as incorrect or incomplete. This leaves as a possible explanation only the valvular origin of the first heart sound. It is apparent that the sounds which originate in valves do not come from the mere closure of the valve but from the sudden tensing of the fibers. Thus the explanation of Schutz and of Frey might be accepted, restricting the region in which the vibrations arise to the structure associated with the valves but excluding the muscle mass. In the dog's heart, ligatured at the auriculoventricular ring, the valvular structures, being supported by the muscle drawn in about them

6. Wiggers, C. J.: Modern Aspects of the Circulation in Health and Disease, Philadelphia, Lea & Febiger, 1923, p. 319.

7. Wolferth, C. C., and Margolies, A.: The Influence of Auricular Systole on the First Heart Sound and the Radial Pulse, Arch. Int. Med. **46**:1048 (Dec.) 1930.

by the ligature, no longer are tautened during systole, and hence no longer set up audible vibrations. If this explanation is correct, the vibrations recorded by Schutz from the surface of the ventricles arose, not in the muscle, but in the valves and were transmitted to the ventricular walls as well as to the blood in the auricles, where similar vibrations were apparent in the pressure curve.

Palfrey [8] and Cabot [9] have noted the similarity between the first sound and that made when a handkerchief, held with one edge in either hand, is suddenly drawn taut. Palfrey, like Schutz, ascribed the first sound to a similar tensing of the ventricular walls. But while it is true that sudden changes in fine fibers, like a string, a handkerchief or even a bit of canvas, will give rise to audible vibrations, it is almost impossible to cause such noises with a piece of thick carpet or with strips of meat as thick as the wall of the left ventricle. That the first sound originates entirely in thin fibrous sheets or bands would be suggested by these simple observations. That it is due to the tensing of the auriculoventricular valves, in a way very similar to the noise produced with the handkerchief in Palfrey's experiment, is suggested by the importance of auricular systole in determining the intensity of the first heart sound.

The variation of the intensity of the first heart sound in cases of complete heart block has been known for many years, frequently recorded in phonocardiograms and discussed at some length by Lewis.[10] In the most complete study, that of Wolferth and Margolies, it was concluded that the "position of the mitral leaflets at the beginning of ventricular systole" was important in modifying the first sound. Wolferth and Margolies [7] observed that intense first sounds were not associated with more vigorous radial pulse waves, and therefore probably not with more vigorous muscular contractions. They did not suggest that the sound originated in the mitral valve, but apparently adhered to the classic theory that it is partly muscular and partly valvular. The reason for less intense sounds, they suggested, was that if ventricular systole occurred when the mitral valve was open, "slight regurgitation might occur, thus retarding the development of intraventricular tension. If, however, the leaflets happened to be near a position of closure at the beginning of ventricular systole, little or no regurgitation might be expected to take place, thus permitting a more rapid rise of intraventricular tension and consequently a louder first sound." Dean [11] has

8. Palfrey, F. W.: The Cause of the First Heart Sound, New England J. Med. **200**:917, 1929.

9. Cabot, R. C.: Physical Diagnosis, New York, William Wood & Company, 1930, p. 172.

10. Lewis, T.: The Relation of Auricular Systole to Heart Sounds and Murmurs, Lectures on the Heart, New York, Paul B. Hoeber, Inc., 1915, p. 53.

11. Dean, A. L., Jr.: Movement of the Mitral Cusps in the Cardiac Cycle, Am. J. Physiol. **40**:206, 1916.

shown that the auriculoventricular valves move from one-third to one-half the distance from wide open to completely closed for a brief moment at the end of auricular systole, but nothing approaching closure of the valves occurs between the onset of the P wave and ventricular systole, even when the P-R interval is 0.24 second. Therefore, the accentuation of the first sound during the interval from 0.05 to 0.23 second after P cannot be due to the auriculoventricular valves being closed.

The explanations of Schutz and of Frey and the analogy offered by Palfrey and Cabot stress the importance of suddenly tensing fibers which were previously under no tension. According to the valvular theory, sound production is due to the sudden rise in tension of the auriculoventricular valves and associated thin fibrous structures occurring when these fibers are slack. If the valves are not only closed but under slight tension from the ventricular side, little or no noise will be caused by further sudden increase in tension. Here, the analogy with the handkerchief is pertinent. If a string or a piece of cloth like a handkerchief is held a little slack between the two hands, and the slack taken out quickly by a light pull, a noise quite similar to the first sound is produced. However, if the slack be taken out gradually by a light pull and then the tension quickly raised even with great force, no noise results. By analogy, whenever ventricular systole occurs at a time when intra-auricular pressure is high and the auriculoventricular valves are not only open but pressed toward the ventricle so as to leave the fibers slack, a sound should arise from suddenly taking the slack out of these thin fibrous structures. If intra-auricular pressure is relatively low, or the ventricle is distended with blood, the auriculoventricular valves may have the slack taken out of them by the relatively high intra-ventricular tension, and hence little or no noise will result with the rise of tension during ventricular systole.

The relation of auricular systole to the intensity of the first sound caused by ventricular contractions occurring at various intervals thereafter is indicated in figure 3. The time relations of auricular pressure and ventricular filling were obtained from Lewis [12] and Wiggers.[13] One of Wiggers' figures [13a] is particularly important, as it shows the effects of a blocked auricular systole without any subsequent ventricular contraction. The intensity of the first sounds occurring at various intervals after the P wave of the electrocardiogram was obtained from three cases recorded in this clinic and those reported by Wolferth and

12. Lewis, T.: Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, Ltd., 1925, p. 47, fig. 24.

13. (*a*) Wiggers, C. J.: Die pathologische Physiologie des Kreislaufs bei Klappenerkrankungen des Herzens, Ergebn. d. Physiol. **29**:262, 1929, fig. 2*b*; (*b*) footnote 6, p. 101, fig. 30.

Margolies[7] and by Schellong.[14] It is obvious that the intensification of the first sound occurs only when auricular pressure and flow into the ventricle are at their peak at the instant the first sound occurs, and that faint sounds occur when rate of outflow from the auricle is low. It should be noted that the second period of accentuation occurred only in young hearts, with relatively rapid ventricular rates and of normal size. In older, slower beating and more diseased hearts the degree of ventricular dilatation was probably sufficient to take the slack out of the auriculoventricular valves at all times except during auricular systole.

The conditions for sound production in mitral heart disease are of particular importance. If the mitral valve is extremely incompetent, a murmur may entirely replace the first sound. In other cases of mitral endocarditis the first sound is accentuated. This is more likely to occur

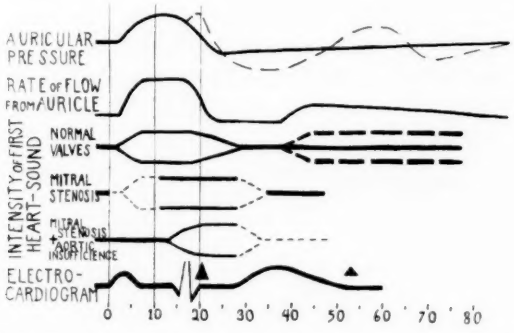


Fig. 3.—The intensity of the first heart sounds occurring at various intervals after the P wave is plotted below the curves of auricular pressure and rate of flow through the auriculoventricular valves (time in hundredths of a second after the onset of P). The dotted line of auricular pressure represents time when ventricular systole occurs normally. The heavy lines indicate pressure and flow with blocked auricular systoles. The normal electrocardiogram and the position of the normal first (large arrow) and second (small arrow) heart sounds are also shown for comparison. The second period of intensification of the first sound in hearts with normal valves, indicated by interrupted lines, has rarely been heard or recorded. It occurred in cases 4 and 5 of Wolferth's and Margolies' series.

if the valve is greatly constricted. Three factors may contribute to this accentuation. In the first place, the ring to which the vibratile fibers attach is rigid, and the taking out of the slack is not buffered by any yielding of these points of attachment. Secondly, the degree of ventricular distention is usually slight, so that an optional degree of slackness may be present. In normal hearts the peak of the intra-auricular pressure curve may be passed shortly before ventricular systole, so that some slack may be taken up before systole occurs. In mitral

14. Schellong, F.: Mitralstenosengeräusch bei Leitungsstörung, Klin. Wchnschr. **8**:2042, 1929.

stenosis the discharge from the auricle is retarded, and the peak of intra-auricular pressure may occur later or be sustained longer than in normal hearts, so that with normal or prolonged conduction time ventricular systole occurs when the mitral valve is still maximally displaced toward the ventricle. It is not possible to state which factor or factors are of greatest importance in causing the accentuated "mitral" first sound, but it is of interest that in mitral stenosis the period of accentuation, in cases with variable P-R intervals, is more prolonged than in normal hearts. Both in Wolferth and Margolies' and in Schellong's [14] cases of mitral stenosis, accentuation was still present when the P-R interval was 0.23 second, while in normal hearts accentuation diminished when the P-R interval was more than 0.14 second in most cases and 0.20 second in all cases. This would seem to favor the prolonged forceful auricular systole as the chief explanation for the accentuated first sound in cases of mitral stenosis with normal conduction. In Wolferth's and Margolies' five patients without lesions of the valve, first sounds were accentuated when the P-R intervals were 0.12 second; with P-R intervals of 0.14 second the accentuation was distinctly less in three cases. As most adults have P-R intervals of 0.14 second or more, this would indicate that the first sounds would be louder if the P-R interval were shortened or if auricular systole lasted 0.02 second longer. A prolongation of the peak of auricular systole by from 0.02 to 0.04 second in the presence of mitral stenosis seems quite probable and is perhaps the chief factor in the accentuation of the first sound.

In this connection another observation of Wolferth and Margolies must be noted. In their case of mitral stenosis and aortic insufficiency, not only was the end of the period of accentuation later than in normal hearts, but the onset of accentuated first sounds occurred much later. The normal first sound is accentuated if it occurs 0.02 second after P, but in this patient no accentuation was apparent until the interval between onset of P and the first sound was 0.13 second. The maximum accentuation, which occurs in normal hearts as early as 0.05 second after P, was found in this case only 0.21 second after P. Margolies and Wolferth suggested that this was due to the mitral stenosis, and quoted Schellong's paper in support of this thesis. An examination of the curves published by Schellong [14] does not bear out this interpretation. The three accentuated sounds are in three different strips with second sounds of different amplitudes. But from a comparison of the degree of accentuation of the loudest and faintest sounds on each strip, it is apparent that the accentuation is nearly as great with a P-R interval of 0.05 second as with one of 0.17 or 0.23 second. In other words, accentuation begins later in a patient with aortic insufficiency plus mitral stenosis, but not in pure mitral stenosis. This suggests that the regurgitation of blood into the left ventricle prolongs

the intervals which must elapse before auricular systole raises the intra-auricular pressure above that in the left ventricle, and hence the period before the auriculoventricular valves are slack enough to permit accentuated first sound production. This is in agreement with the experimental observations of Wiggers,[15] who found that aortic regurgitation could alter the outflow through the mitral valve.

SUMMARY

Experiments on the exposed hearts of dogs demonstrate that there is no muscular element in the first heart sound, and that ventricular systole produces no audible vibrations, in either empty or full hearts, if tensing of the auriculoventricular valves is prevented.

A comparison of the pressure changes in the auricles and the rate of outflow through the atrioventricular valves with the period at which first sounds are accentuated by a previous auricular systole shows the importance of the position of the auriculoventricular valves in determining the loudness of the first sound. If the valves are closed and intraventricular pressure about as high as that in the auricle, ventricular systole causes only a faint sound; if the valves are slack and displaced toward the ventricle by the rush of blood through them, ventricular systole produces a loud first sound.

CONCLUSION

The first heart sound is due to suddenly putting under high tension the previously slack fibers of the auriculoventricular valves. If the valves are closed and the slackness taken up gradually before ventricular systole occurs, the intensity of the sound is greatly diminished. The factors determining loudness of the first sound are, therefore: the degree of tension in the valves when ventricular systole occurs and (less important) the rate of rise of intraventricular tension.

---

15. Wiggers, C. J., and Green, H.: Experimental Aortic Insufficiency: Regurgitation Maximum and Mechanisms for Its Accommodation Within Mammalian Ventricle, Proc. Soc. Exper. Biol. & Med. **27**:599, 1930. Wiggers, C. J., and Maltby, A. B.: Hemodynamic Factors Determining the Characteristic Changes in Aortic and Ventricular Pressure Pulses in Experimental Aortic Insufficiency, Am. J. Physiol. **97**:689, 1931.

CYTOPLASMIC CHANGES IN CIRCULATING LEUKOCYTES IN INFECTION

CHARLES J. SUTRO, M.D.
NEW YORK

The severity of infection can be estimated by a study of the cellular elements of the peripheral blood stream. The number of circulating leukocytes and the differential percentage of each type have until now been given the greatest attention. It is accepted that a leukopenia in a severe infection, which usually induces a marked leukocytosis (pneumonia), often forewarns of a poor or fatal prognosis. On the other hand, there are many systemic infections in which leukopenia is the rule but nevertheless the prognosis in general is good. Thus, the quantitative estimation of leukocytes certainly appears not to be the most important factor in the gaging of the prognosis.

The differential count varies with the different types of infection. In allergic infections, an eosinophilia may be present; in tuberculosis, a monocytosis is usually found; in very severe suppurative infections, myelocytes are noted; in subacute bacterial endocarditis (Streptococcus viridans), small numbers of macrophages may be found in the peripheral blood, especially if the blood is obtained from the lobe of the ear.

Arneth [1] directed attention to variations in the nuclear configurations of the granulocytes. His method of classifying such variations was cumbersome and too complicated for general application in the routine clinical laboratory. Schilling [2] devised a simplified scheme for tabulating the various forms of the granulocytic cells, namely, the myelocytes, the young polymorphonuclears, the staff (band) polymorphonuclears and segmented polymorphonuclears. The relative percentage of each in the blood of a normal adult is given as follows: myelocytes, none; young polymorphonuclears, 1 per cent; staff polymorphonuclears, from 1 to 4 per cent, and segmented neutrophilic polymorphonuclears, from 60 to 70 per cent. In infections, there is usually an increase in the young and staff or band forms, which changes Schilling designated as "shift to the left." A somewhat simpler method of designating

From the Laboratory Division and Wards of the Hospital for Joint Diseases.

1. Arneth, J.: Die neutrophilen Leukozyten bei Infectionskrankheiten, Deutsche med. Wchnschr. **30**:54, 1904; Die qualitative Blutlehre, Leipzig, Dr. Werner Klinkhardt, 1920.

2. Schilling, V.: Das Blutbild und seine klinische Verwertung, ed. 7-8, Jena, Gustav Fischer, 1929.

polymorphonuclear cells was suggested by Pons and Krumbhaar.[3] They divided the polymorphonuclear cells into nonsegmented and segmented types. The severity of infection may furthermore be reflected by changes in the polymorphonuclear cells. Basophilic cytoplasmic granules, which have been designated as "toxic granules,"[4] appear. They are numerous, small in size, and rarely situated in the nuclear zone. These characteristics distinguish them from the granules of the basophilic polymorphonuclear cells. In addition, the entire cytoplasm, in severe infections, may show affinity for the basophilic stain (fig. 1). Furthermore, the segmented polymorphonulear leukocytes occasionally show vacuoles in the cytoplasm (fig. 2). The presence of toxic granules and the degeneration of the cytoplasm of the granulocytic cells have been emphasized in the German literature, and more recently in this country by Rosenwasser and Rosenthal,[5] Kugel and Rosenthal[6] and Rosenthal and Sutro.[7]

So far, all such studies have been made with the use of special stains or buffered solutions, with either Wright or Jenner-Giemsa stains. In this study, which was undertaken in the hope of applying the investigation of cytoplasmic changes to routine examination, stock Wright stains were used. The air fixed slide was stained for one minute, and distilled water was added for three minutes. The slide was dried in air and examined with the ordinary oil immersion objective. In order to settle all doubts and to exclude the possibility that precipitated stain

3. Pons, C., and Krumbhaar, E. B.: Studies in Blood Cell Morphology and Function: III. Extreme Neutrophilic Leukocytosis, with a Note on a Simplified Arneth Count, J. Lab. & Clin. Med. **10**:123, 1924.

4. Cesaris-Demel, A.: Ueber die morphologische Struktur und die morphologischen und chromatischen Veränderungen der Leukozyten, auf Grund von Untersuchungen nach der Methode der Vitalfarbung des Blutes, Virchows Arch. f. path. Anat. **195**:1, 1909. Turk, W.: Vorlesungen ueber klinische Haematologie, Vienna, W. Braumueller, 1912. Naegeli, O.: Blut-Krankheiten und Blutdiagnostik, ed. 4, Berlin, Julius Springer, 1923. Alder, A., and Schleip, K.: Atlas der Blut-Krankheiten, ed. 2, Berlin, Urban & Schwarzenberg, 1928. Gloor, W.: Die klinische Bedeutung der qualitativen Veränderung der Leukozyten, Leipzig, Georg Thieme, 1929. Mommsen, H.: Die Granula der polymorphkeringen feingekörnten Leukozyten unter normalen und pathologischen Verhältnissen ihre gesetzmässigen Beziehungen zum Ablauf akuter Infektionen, Ztschr. f. d. ges. Exper. Med. **65**:287, 1929; Die Pathologische (toxische) Granulation der feingekörnten Leukocyten, ihre objektive Erkennung und praktisch klinische Verwertung, Klin. Wchnschr. **42**:2420, 1929.

5. Rosenwasser, H., and Rosenthal, N.: The Blood Picture in Otitic Infections, Arch. Otolaryng. **14**:291 (Sept.) 1931.

6. Kugel, M. A., and Rosenthal, N.: Pathological Changes in Polymorphonuclear Leukocytes During Progress of Infections, Am. J. M. Sc. **183**:657, 1932.

7. Rosenthal, N., and Sutro, Charles J.: Am. J. Clin. Path. **3**:181 (May) 1933.

was being interpreted as granules, the patient's blood was placed on one portion of the slide and blood from a healthy control was smeared on another portion of the slide. Thus, the control and unknown blood

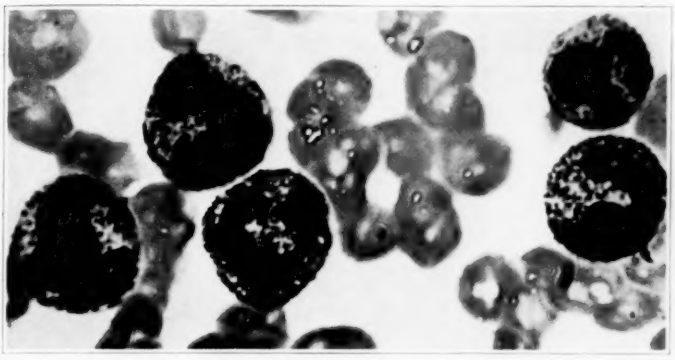


Fig. 1.—Streptococcus peritonitis (Wright stain). Toxic granules are seen in all the polymorphonuclear cells (absent in the control slide).

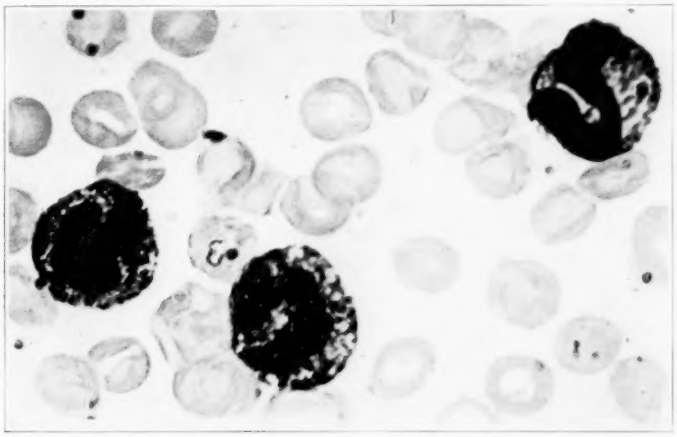


Fig. 2.—Lobar pneumonia (Wright stain). Toxic granules and vacuoles are shown. The vacuoles are particularly prominent in the lowermost leukocyte.

are stained together. All difficulty in interpretation of the granules is definitely settled.

The present report is based on a study of about two hundred cases. The hemoglobin determination, red cell count, leukocyte count and differential studies were made. The polymorphonuclear cells were tabu-

lated as nonsegmented and segmented, according to the method of Pons and Krumbhaar. The results were tabulated as shown in the accompanying table, according to the suggestion of Kugel and Rosenthal.

The "degenerative index" enables one, more or less, to judge accurately the severity of the infection or intoxication from which the patient is suffering. Illustrative group cases given here show the value of estimating the degenerative index.

REPORT OF CASES

CASE 1.—Dr. T. was admitted to the hospital on May 7, 1932, complaining of severe pain in the lower right side of the chest and of fever. During 1922, for a period of four months, he had mild pains in the chest and profuse expectoration of foul sputum. Prior to 1922, he had suffered considerable exposure to x-rays and had lost one of his fingers due to a severe roentgen burn. A roentgenographic

Hemogram *

	Nontoxic	Toxic	Total
Neutrophil polymorphonuclear cells			
Nonsegmented	15	25	40
Segmented	30	20	50
Total	45	45	90
Lymphocytes	8		
Monocytes	2		
Eosinophilic polymorphonuclears			
Basophilic polymorphonuclears			
Myeloblasts			
Myelocytes			
Macrophages			

Toxic polymorphonuclear cells	45	1
Total polymorphonuclear cells	90	2

Degenerative index = ++

* The number of toxic polymorphonuclear cells divided by the total number of polymorphonuclear cells is the "degenerative index." 1 = 4 plus; ¾ = 3 plus; ½ = 2 plus, and ¼ = 1 plus. When the results are in between these figures, the "degenerative index" is approximate. However, a four plus is never diagnosed, except when all the cells show basophilic granules.

plate of the patient's chest on admission revealed a solid mass extending from the apex to the base on the right side, almost suggesting solid carcinoma. The leukocyte count was 12,000; 88 per cent of polymorphonuclears were present and there was a four plus degenerative index. The presence of these toxic granules in all polymorphonuclear cells suggested severe infection or an ulcerative type of carcinoma. Postmortem examination one day later showed a lobar pneumonia which extended from the apex to the base.

It is accepted that toxic granules are found in all cases of lobar pneumonia in adults with or without pleural effusion, and in the absence of toxic granules it is hazardous to make a diagnosis of lobar pneumonia.[7] However, in pulmonary diseases, such as mild tuberculosis, rheumatic fever, draining lung abscess or in nonulcerating carcinoma, toxic granules are usually absent, and give at the most a one plus index. It is interesting that patients receiving deep roentgen therapy will often show a four plus index, owing possibly to protein destruction and to a marked absorption. Cases of ulcerating carcinomas will also show high degenerative indexes.

Case 2.—E. B., a girl, aged 19, was admitted to the hospital with a history of terrific lower abdominal pain and irregular menses. Blood examination prior to operation revealed a slight leukocytosis of 12,000, and a slight increase in the polymorphonuclear neutrophils to 75 per cent, but the absence of toxic granules. Two days after operation, at which a chronically inflamed appendix was removed, there developed a sudden rise in temperature to 104.8 F. The blood count showed 8,000 leukocytes, but 29 per cent were segmented polymorphonuclear cells, and the degenerative index was two plus (April 12). On April 13, the white count was 6,000, with 45 per cent nonsegmented polymorphonuclear cells and an index of four plus. On April 18, the white count rose to 18,000; the nonsegmented cells were 40 per cent, and the degenerative index was four plus. On April 20, another count showed 13,700 leukocytes, 35 per cent nonsegmented polymorphonuclear cells and four plus toxic granules. The patient died, and during her stormy clinical course, showed definite evidences of peritonitis. A blood culture four days before death was positive for the hemolytic streptococcus.

It is important to note that in acute abdominal conditions, when the lesion is still localized, as for instance, in acute appendicitis or in acute cholecystitis, toxic granules in the cytoplasm of polymorphonuclear cells are unusual. However, when they appear, complications such as pylephlebitis, ruptured abscess, peritonitis or bacteremia must be suspected. In children with undiagnosed intra-abdominal complaints, but with a blood picture showing toxic granules in all polymorphonuclear cells, pneumonia, bacteremia or possible metastatic septic foci must be suspected.

Case 3.—A boy, aged 6 years, was admitted to the hospital with a diagnosis of bilateral suppurative ethmoiditis. Physical examination revealed bilateral swelling of the periorbital tissues and tenderness over the ethmoid regions. A blood count showed 17,900 leukocytes, and a differential count showed 20 per cent nonsegmented and 56 per cent segmented polymorphonuclear cells, 21 per cent lymphocytes and 3 per cent monocytes. The degenerative index was four plus. Blood culture was positive for Streptococcus viridans. A radical frontal sinusectomy was performed. The pus obtained from the ethmoid area contained green-producing streptococci. Seven days after operation, the leukocyte count was 11,400, and there were 61 per cent polymorphonuclear cells and 39 per cent lymphocytes. Basophilic toxic granules were absent. The patient made an uneventful recovery.

In this case, as so often happens in cases of bacteremia, a four plus degenerative index was noted even before the results of the bacteriologic examination was reported. Most of the protracted generalized infections, with the exception of subacute bacterial endocarditis and miliary tuberculosis, cause the appearance of toxic granules, and the blood cultures show bacteria less constantly. However, in the pre-agonal state, toxic granules may be found in practically all infections, as in a case of subacute bacterial endocarditis, a two plus degenerative index was observed two days prior to death; the explanation for this was evident at postmortem examination, for in addition to the subacute bacterial endocarditis, bronchopneumonia was found. In very septic patients without toxic granules in the leukocytes and with negative serum agglu-

tination tests and negative blood cultures, one should think of miliary tuberculosis, subacute endocarditis (bacteria-free) or rheumatic fever.

Case 4.—V. C., a girl, aged 12 years, was admitted to the hospital with the history of a painful discharging ear of one week's duration. There had been chills and fever ranging from 102 to 104 F. On April 11, one day prior to mastoidectomy, the total leukocyte count was 19,000 with 82 per cent polymorphonuclear cells, but no toxic granules were present. Two days after the operation, the temperature was still 104 F., and the leukocyte count dropped to 14,700 cells per cubic millimeter, but the differential count showed 14 per cent nonsegmented forms and 54 per cent segmented forms. At this time, all of the polymorphonuclear cells showed toxic granules. The high degenerative index suggested the presence of either a sinus thrombosis or pneumonia, or possibly both. Blood cultures were sterile on two occasions. On April 15, roentgen studies showed pneumonia of both upper lobes. On April 22, blood examination revealed 27,800 white cells with 91 per cent polymorphonuclear cells. The degenerative index was still four plus. The steady high index intimated a very poor prognosis. The patient died on April 30.

Postmortem examination revealed a free sigmoid sinus without any evidence of thrombosis. In the lungs, gangrenous metastatic pyemic abscesses were found in all lobes, especially on the left, with multiple perforations into the left pleural cavity and the presence therein of an empyemic foul-smelling mass of pus. In addition, there was a complete compression atelectasis of the left lower lobe and emphysema of the right lung with fresh abscesses. A small interlobar empyema was found. An embolus was seen in one of the bronchial arteries.

This case emphasizes the fact that the degenerative index may be four plus, and yet no positive blood culture could be obtained in a case that was definitely one of bacteremia. The blood in otitis media or mastoiditis shows few or no toxic granules. A sudden appearance of toxic granules in such cases signifies an overwhelming infection, such as sinus thrombosis, pneumonia or metastatic pyogenic foci.[8]

Case 5.—H. P., aged 30, presented symptoms and signs of chronic cholecystitis. Blood examination prior to operation revealed nothing unusual. Three days after the laparotomy, the temperature rose suddenly to 103 F. The blood count showed 43,000 leukocytes per cubic millimeter, with 92 per cent polymorphonuclear cells and a three plus degenerative index. Six days later, the abdominal wound broke open from a necrotizing infection. After proper surgical treatment, the leukocytes became reduced to 32,000 and the degenerative index was two plus. Five days later, the leukocyte count was 9,800, and all toxic granules disappeared. The patient made an excellent recovery. Recovery was anticipated because the degenerative index became reduced, rather than four plus, but nevertheless the patient had a stormy course.

Case 5 may now be contrasted with case 6.

Case 6.—O. C., a boy, aged 11 years, had a scar due to an old burn on his right knee. A pedicle skin flap plastic operation was done. Blood examination before operation revealed nothing abnormal. Postoperatively, the temperature rose suddenly to 105 F. Blood examination at this time showed a leukocyte count of 44,000,

8. Footnotes 5, 6 and 7.

with 19 per cent nonsegmented forms and 69 per cent segmented forms, and the absence of toxic granules. At no time did the patient appear desperately ill. Forty-eight hours later, the patient was able to get out of bed, in spite of a leukocyte count of 28,100.

In retrospect, these two cases corroborate the importance of looking for toxic granules, for in spite of the fact that both patients had high leukocytosis, their clinical courses were divergent, as the second patient did not show toxic granules.

Case 7.—A. G. came to the hospital complaining of a swollen left leg, which existed for two months. Physical examination revealed a brawny indurated left leg. Prior to operation, the blood examination showed nothing unusual. Laparotomy revealed a large retroperitoneal tumor, which on microscopic examination was carcinoma. Five days after the operation, the temperature rose to 105 F. The wound revealed the presence of foul-smelling necrotic tissue. All subsequent dressings showed a sanguineous discharge and contained tissue masses. The absorption in association with the tissue necrosis was probably of importance in the induction of a three plus degenerative index. With cessation of discharge from the wound and the return of the temperature to normal, the degenerative index became reduced to one plus. The patient was much improved and was discharged one week later.

CONCLUSION

In a study of two hundred cases in which the blood was investigated for toxic granules, it was found that the continued presence of a four plus degenerative index would indicate a serious prognosis. A four plus degenerative index in cases in which bacteremia or pyemia is suspected points to generalized infection in spite of a negative blood culture. In local infections (mastoiditis, acute appendicitis, etc.) without complications, there will be no toxic granules, or at most the degenerative index will be one or two plus. However, should these conditions be complicated by bacteremia or peritonitis, toxic granules appear in many or all of the polymorphonuclear cells.

SYPHILIS OF THE STOMACH

WITH SPECIAL REFERENCE TO THE SIGNIFICANCE OF SPIROCHETES

HARRY A. SINGER, M.D.
CHICAGO

The presence in gastric lesions of spirochetes having the morphologic characteristics of Spirochaetae pallidae is generally considered proof positive that the underlying disease is syphilitic. Even when the histologic changes are not syphilitic in type the occurrence of these spirochetes, according to current view, stamps the process as syphilitic. The correctness of these statements can be readily affirmed by reference to almost any text or periodical dealing with gastric syphilis. Luria,[1] whose monograph represents the most comprehensive and recent survey of the subject, after emphasizing the difficulties in distinguishing, by histologic means alone, syphilitic from other gastric lesions, wrote:

> It would be particularly valuable, therefore, if one were to succeed in finding spirochetes in microscopic sections of the stomach, especially in specimens obtained by operation. Such a finding furnishes naturally unequivocal proof of the syphilitic origin of the pathological process and helps to interpret the histological picture in questionable cases.

The propriety of attaching diagnostic significance to the mere presence of spirochetes morphologically resembling Spirochaetae pallidae has been subjected to but limited scrutiny. In 1928, in collaboration with Dr. F. G. Dyas,[2] I reported a case of gastric syphilis in which spirochetes were found but were not considered syphilitic. It was pointed out at that time that the presence of spiral organisms did not necessarily mean infection by Spirochaeta pallida. It was stated that in an examination limited to the morphologic characteristics of organisms little weight could be placed on the distinguishing features on account of the close resemblance between the syphilitic and saprophytic spirochetes. Reference was made to the organisms demonstrated by

---

From the Department of Medicine, University of Illinois College of Medicine, and the Department of Pathology, Cook County Hospital.

1. Luria, R.: Syphilitische und syphilogene Magenerkrankungen (Gastrolues), Arch. f. Verdauungskr. (supp.) **46**:1, 1929.

2. Singer, H. A., and Dyas, F. G.: Syphilis of the Stomach with Special Reference to Certain Diagnostic Criteria, Arch. Int. Med. **42**:718 (Nov.) 1928.

Pilot and Davis [3] in Levaditi preparations of lungs with abscess and gangrene, in which the spirochetes, although of oral origin, presented the typical appearance of Spirochaetae pallidae. While the article by Dyas and myself was in press a report appeared by Welch [4] in which the syphilitic nature of the spirochetes pictured by McNee [5] was questioned and the opinion expressed that they might have been secondary invaders.

In writings on gastric syphilis up to 1928 no one, with the exception of Schmorl,[6] whose comment in 1907 has been entirely overlooked, apparently investigated the significance of spirochetes in syphilis of the stomach. It was presumably taken for granted that any spirochete present possessing the typical morphology was Spirochaeta pallida. As a matter of fact, the statements of Dyas and myself to the contrary have seemed so heterodoxical that they have been entirely disregarded or looked on askance. O'Leary,[7] whose experience includes the study of eighty-nine cases of gastric syphilis, wrote with regard to the specificity of demonstrable spirochetes: "Singer and Dyas doubted that the organisms found by McNee were Spirochaeta pallida, and expressed the belief that they were Vincent's spirilla.[8] Hartwell, however, accepted McNee's observation as authentic." O'Leary, in making this statement, evidently inferred that we were incorrect in denying the specificity of McNee's organisms, for he continued to assert: "Warthin reported that he has demonstrated the Spirochaeta pallida in eight cases of gastric syphilis in practically all of which operation was done because of a diagnosis of peptic ulcer. The incidence of the demonstration of Spirochaeta pallida in the gastric ulcer of the gummatous type no doubt will be higher in the hands of pathologists who become expert in its identification."

The question of the nature of the spirochetes demonstrated in lesions of the stomach is not only of scientific but also of practical importance. First, with regard to diseases presenting the histologic characteristics of syphilis: The only case in which spirochetes interpreted as of the

3. Pilot, I., and Davis, D. J.: Studies in Fusiform Bacilli and Spirochetes, Arch. Int. Med. **34**:313 (Sept.) 1924. Pilot, I.; Davis, D. J., and Shapiro, J. J.: Studies on Fusiform Bacilli and Spirochetes, Am. Rev. Tuberc. **8**:249 (Nov.) 1923.

4. Welch, A. S.: Diagnosis of Syphilis of the Stomach, Am. J. Syph. **12**: 325 (July) 1928.

5. McNee, J. W.: Syphilis of the Stomach, Quart. J. Med. **15**:215, 1921.

6. Schmorl, in discussion of Jores, L.: Demonstration von gummöser Magensyphilis, Verhandl. d. deutsch. path. Gesellsch. **11**:319, 1907.

7. O'Leary, P. A.: Gastric Syphilis: Data Accumulated from 89 Cases, Am. J. Surg. **11**:286 (Feb.) 1931.

8. We [2] used the term Vincent in a broad sense to refer to the various saprophytic organisms of the oral origin.

pallida type were demonstrated in a stomach histologically syphilitic is, as will be submitted later, that of McNee.[5] If spirochetes occurring in such numbers as pictured by McNee are of the pallida type, the organism should be demonstrable in at least a fairly high percentage of other syphilitic stomachs. In this event, the presence or absence of spirochetes should decide the diagnosis. If the demonstration of the organism is the basic criterion, none of the many other cases reported as gastric syphilis can be accepted. The conclusion which follows is that syphilis of the stomach is an exceedingly rare disease. The corollary to this would be that numerous patients are receiving antisyphilitic treatment unnecessarily. On the other hand, if the spirochetes portrayed by McNee can be shown to be nonsyphilitic, it is reasonable to assume that the absence of spirochetes does not militate against the diagnosis and that the therapeutic response should continue to constitute the chief diagnostic criterion and to indicate the treatment required. The second type of gastric lesion in which spirochetes considered syphilitic were found is the chronic peptic ulcer. The only author, as will be shown later, who has demonstrated spirochetes identified as syphilitic in what were apparently peptic ulcers is Warthin.[9] If Warthin's bacterioscopic interpretation in these cases, which would otherwise have been considered simple ulcer is correct, it can be assumed that a fair proportion of so-called peptic ulcers are syphilitic. It would also indicate that an examination limited to the anatomic features of a lesion, even though it showed typical chronic round ulcer, is insufficient as a basis for diagnosis; also that Levaditi preparations are indispensable. If, on the other hand, Warthin's spirochetes can be shown to be nonsyphilitic, it would follow that the cases of peptic ulcer ascribed by many to syphilis are probably nonsyphilitic and do not indicate antisyphilitic therapy.

In reviewing the literature, one is struck by the paucity of material on the subject of the significance of spirochetes in the stomach. However, the available reports are quite conclusive. Schmorl,[6] in 1907, pointed out that differentiation of syphilitic spirochetes from other, similar organisms in silver preparations was often impossible. He deplored the fact that the brilliant discovery of Schaudinn advanced the pathologic knowledge of syphilis only slightly, for in questionable cases, particularly, either the demonstration of the spirochete was unsuccessful or, when present, the pallida could not be distinguished readily from other types. The presence of spirochetes in the stomachs of nonsyphilitic subjects was clearly demonstrated in 1908 by

9. Warthin, A. S.: Syphilis of the Smaller Arteries, New York M. J. **115**:69 (Jan. 18) 1922.

Simmonds.[10] He found in degenerating carcinomas spiral organisms which he stated had their origin in the flora of the mouth. He asserted that the spirochetes were found not alone on the surface but also in the tissues. He concluded that their presence was of significance in that they might be confounded with those of syphilis. In the discussion which followed, Fraenkel[11] stated that many of the spirochetes portrayed by Simmonds could not be differentiated from those causing syphilis.

The early observations of Schmorl, Simmonds and Fraenkel, to the effect that spirochetes originating in the mouth were present in the gastric wall and were practically indistinguishable from the specific organism of syphilis, have received ample substantiation. With regard to incidence, the frequent occurrence in the lumen of the stomach of spirochetes derived from the oral cavity has been firmly established by Luger and Newberger,[12] especially in connection with carcinoma. In sixteen cases of malignant gastric conditions studied by them the aspirated contents of the stomach after fasting showed in eleven a more or less rich spirochetal flora. Direct smears from the surface of five gastric carcinomas showed enormous numbers of spirochetes in all. With regard to the morphologic differentiation, bacteriologists are agreed that the resemblance between specific and certain saprophytic spirochetes is an extremely close one. Park and Williams,[13] whose recent text can be considered authoritative, indicated that the differences between Spirochaeta pallida and for instance Treponema dentium are merely relative and not absolute. Erich Hoffman,[14] with whom Schaudinn discovered Spirochaeta pallida in 1905, expressed the opinion that a differentiation of the pallida type from morphologically similar types (which he offered to designate as Spirochaeta pseudopallida) demands further study.

The differences between syphilitic and saprophytic spirochetes in stained smears and hanging drops are even less apparent in histologic preparations. The lack of detail of Spirochaeta pallida in tissues impregnated with silver is quite apparent when compared with dark-

10. Simmonds: Ueber Spirochäten Befunde in Karzinomen, München. med. Wchnschr. **55**:1103, 1908.

11. Fraenkel, E., in discussion of Simmonds (footnote 10).

12. Luger, A., and Newberger, H.: Ueber Spirochäten-Befunde im Magensaft bei Carcinoma ventriculi, Wien. med. Wchnschr. **70**:1254 (July 3) 1920.

13. Park, W. H.; Williams, A. W., and Krumwiede, C.: Pathogenic Microorganisms, ed. 8, Philadelphia, Lea & Febiger, 1924, p. 529.

14. Hoffman, E., and Hofmann, E.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1927, vol. 15, pt. 1, p. 87.

field preparations and smears (Noguchi [15]). Pilot and Davis,[6] who have made a comprehensive study of spirochetes of the mouth in pulmonary abscess and gangrene, consider the differentiation between saprophytic spirochetes and Spirochaetae pallidae in silver preparations very difficult and at times impossible. Comparison between spirochetes in Levaditi stains of nonsyphilitic lesions of the stomach and known Spirochaetae pallidae lends substantiation to the views already expressed. Figures 1 and 2 are photomicrographs from a necrotizing, ulcerating

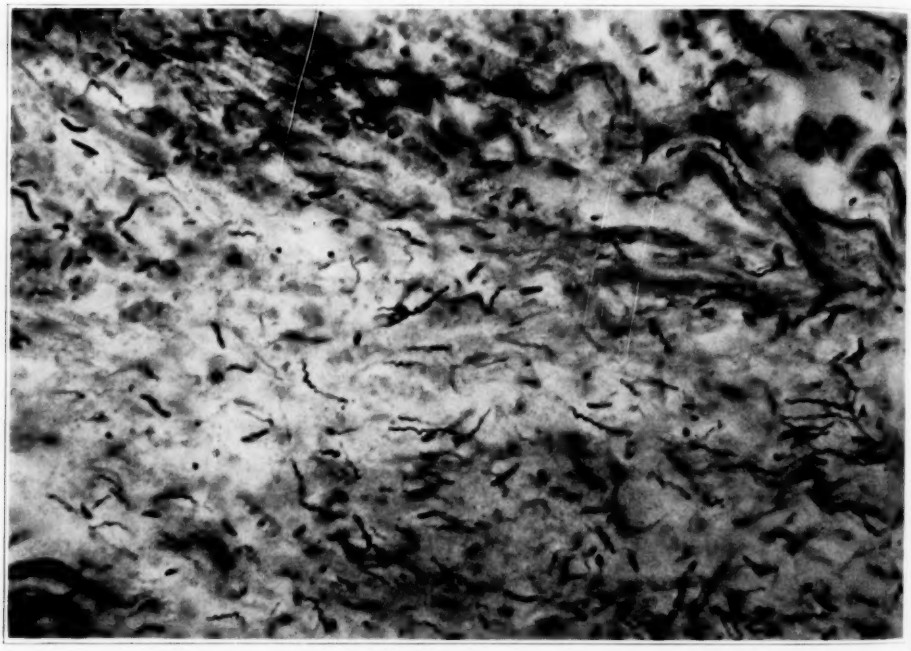


Fig. 1.—Levaditi preparation of a section taken from the superficial portion of a necrotizing, ulcerating carcinoma of the stomach encountered at autopsy. No indication of syphilis was found during life or at postmortem examination. The spirochetes, which in many instances resemble Spirochaeta pallida, are saprophytic and are derived from the mouth. Fusiform bacilli are found in association with the spirochetes. This photomicrograph has not been retouched.

carcinoma of the stomach obtained at autopsy. The argentaffine organisms present are almost unquestionably of oral origin, for there was no clinical, serologic or anatomic evidence of a syphilitic infection.

15. Noguchi, H.: The Spirochetes, in Jordan, E. O., and Falk, I. S.: The Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, p. 452.

The resemblance of the oral spirochetes in nonspecific ulcerating lesions of the stomach to Spirochaeta pallida is apparent in these representative illustrations.

In spite of the large number of cases of syphilis of the stomach which have been reported, only a few contain mention of the presence of spirochetes.[16] Even the large series of ninety-three cases recorded by Eusterman [17] does not include a single one in which the spirochete was found. Reference is made particularly by foreign authors to several articles in English dealing with spirochetes, but most of these reports are misquoted or misinterpreted. Boas [18] mentioned Wile and Allbutt, and Luria [1] referred to the latter two and also to LeWald as having found Spirochaeta pallida in the tissues. Investigation of the original articles indicates that Wile [19] simply made reference to a case of Warthin's, whereas Allbutt [20] and LeWald [21] described McNee's case. Several writers, both foreign and native, have referred to Welch's [4] case as one in which the Spirochaeta pallida was demonstrated. It is true that Welch stated: "In one of many blocks we found spiral bodies characteristic of Treponema pallidum. The preparation was passed on by several competent men, who could give no reason why the bodies seen were not Treponema pallidum." His object was to emphasize the difficulty in recognizing the causative organism of syphilis, for in the next sentence he wrote: "Under a high-powered microscope, Dr. H. R. Wahl, Professor of Pathology at the University of Kansas, showed that one of the most characteristic bodies was part of the so-called elastic membrane of a blood vessel." The only authors, so far as has been ascertained, who have succeeded in identifying in gastric lesions, spirochetes which were considered syphilitic are McNee and Warthin. The correctness of the morphologic diagnosis of the organisms demonstrated by these two writers has hardly been brought into question.

---

16. This statement and similar ones in the article refer solely to cases of gastric syphilis of clinical importance, and exclude the instances of congenital syphilis in the new-born.

17. Eusterman, G. B.: Gastric Syphilis, Observations Based on 93 Cases, J. A. M. A. **96**:173 (Jan. 17) 1931.

18. Boas, K.: Syphilogene Erkrankungen des Magens im Lichte moderner Forschungsergebnisse, Zentralbl. f. Haut- u. Geschlechtskr. **13**:1, 1924.

19. Wile, U. J.: Visceral Syphilis: Syphilis of the Stomach, Arch. Dermat. & Syph. **1**:543 (May) 1920; Visceral Syphilis: Syphilis of the Intestine, ibid. **3**: 372 (April) 1921.

20. Allbutt, T. C.: Visceral Syphilis, Especially of the Central Nervous System and Cardiovascular System, Brit. M. J. **2**:177 (Aug. 6) 1921.

21. LeWald, L. T.: Leather-Bottle Stomach (Linitis Plastica), Am. J. Roentgenol. **8**:163 (April) 1921.

The doubt previously expressed regarding the syphilitic nature of the spirochetes in cases of acquired gastric syphilis having been overlooked or the basis for question considered inadequate, it appears desirable to analyze the facts given in connection with each report. The classic example of Spirochaeta pallida in a syphilitic stomach is that of McNee.[5] The accompanying photomicrograph (fig. 3) illustrates why it has met with general acceptance, for at first glance the picture is typical of the spirochetes of syphilis. However, there are several reasons for assuming that the organisms are derived from the oral flora. In the first place, in tertiary lesions of acquired syphilis a paucity of organisms is characteristic. The discovery of an occasional organism generally requires a painstaking, laborious search. The presence of many spirochetes is typical of a nonsyphilitic infection. In McNee's case in a single microscopic field (oil immersion) at least eighteen distinct spirochetes are represented. Furthermore, in an infection due to syphilis the spirochetes are unassociated with any other organisms. In nonsyphilitic lesions, on the other hand, in which saprophytic spirochetes invade the tissues, other micro-organisms, especially fusiform bacilli, are found in combination. The spirochetes, however, tend to migrate beyond the bacilli and to occupy an advanced zone (see Pilot and Davis[3]). McNee's observations answer to the latter description, for he wrote: "Near the free surface the spirochetes in the necrotic surface layer were mixed with other organisms, but in the deeper granulation tissue close to the muscular coat they were unaccompanied by any other demonstrable organism." Another important consideration is the type of tissue in which the spirochetes were found. As pointed out, saprophytic spirochetes of the mouth, which for all practical purposes are morphologically indistinguishable from the pallida type, are found in degenerated tissue of the gastro-intestinal tract with regularity. In order to be valid, Spirochaetae pallidae should be observed more or less remotely from necrotic areas. However, the block containing the spirochetes was taken from an area manifestly necrotic, judging from the photograph accompanying the article and also from McNee's own description. Finally, it should be taken into account also that of eight blocks of tissue from known situations which were stained according to Levaditi's method only one revealed spirochetes. Syphilis would hardly be expected to show Spirochetae pallidae localized to only one area of a granulomatous infiltrate of hematogenous origin. However, if one assumes that the organisms found represented secondary invaders and were not primarily responsible for the extensive lesion, the explanation becomes apparent.

McNee is most frequently cited in connection with syphilis of the stomach and spirochetes because of his convincing illustration rather

than the number of cases, for he reported but one instance. Warthin,[22] who has observed eight cases, is mentioned less frequently probably because he has published the details of none and, so far as can be ascertained, has not reproduced by photograph the spirochetes observed. In a paper [9] dealing with syphilis of the smaller arteries he made the statement that specific inflammation of the gastric and duodenal arterial branches is an undoubted factor in the production of peptic ulcer. He wrote: "We have had three cases of syphilitic peptic ulcer of the stomach. In one of these, from Dr. Cabot's service, the syphilitic vascular disease was very pronounced, and the neighboring lymph nodes showed active syphilitic lesions. Spirochetes were found in numbers, both in the perivascular infiltrations of the stomach wall and in the lymph nodes." This same case was referred to in a previous publication from the University of Michigan by Wile,[19] who recorded that the Wassermann reaction was negative. In a more recent paper by Warthin [22] dealing with the relationship of gastric carcinoma and ulcer he merely mentioned the fact that he had had "eight cases of ulcer of the stomach that are definitely shown to be syphilis." These eight cases are referred to by both O'Leary [7] and Eusterman [17] as proved cases of peptic ulcer of syphilitic origin.

The weight of Warthin's authority on the subject of syphilis and especially on that phase dealing with spirochetes tends to lead many to accept his statements without hesitation. The syphilitic origin of peptic ulcer, however, is seriously questioned by most authorities on gastric syphilis. Konjetzny,[23] whose chapter on syphilis of the stomach in Henke's and Lubarsch's system of pathology probably represents the current opinion, denies the existence of peptic ulcer due to syphilis. He corroborates the view of E. Fraenkel [24] and Lubarsch,[25] that the vascular changes described in connection with these lesions and ascribed to syphilis are not specific but can be found in simple ulcers. In the anatomic study of established cases of syphilis of the stomach, one gains the impression that the syphilitic infiltration is primary and that ulceration is secondary. The striking differences between peptic ulceration, which is primary, and syphilitic ulceration, which appears to be secondary to an infiltrate, is well illustrated in an article by

22. Warthin, A. S.: The Relation of Cancer of the Stomach to Ulcer, Proc. Inter-State Post-Grad. M. Assemb., North America, Oct. 17-21, 1927, p. 162.

23. Konjetzny, G. E.: Die Entzündung des Magens, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1928, vol. 7, pt. 2, p. 1015.

24. Fraenkel, E.: Zur Lehre von der acquirierten Magen-Darmsyphilis, Virchows Arch. f. path. Anat. **155**:507, 1899.

25. Lubarsch, O., quoted by Baumecker, H.: Die klinische Diagnose der hypertropischen Magenlues, Med. Klin. **26**:1557 (Oct. 17) 1930.

Fig. 2.—This preparation is from the same section as that in figure 1 but somewhat deeper. The spirochetes have migrated beyond the necrotic surface layer in advance of the fusiform bacilli. This photomicrograph has not been retouched.

Fig. 3.—McNee's illustration of a retouched photomicrograph of a section from a case of gastric syphilis (see text), stain by Levaditi's method (reproduced from *British Journal of Surgery* [supp.] **14**:100, 1927).

Brams.[26] The occurrence of spirochetes in the wall of an ulcer has little significance per se. The presence of spirochetes in limited numbers was demonstrated in the gastric contents of patients with ulcer by Luger and Newberger.[12] Spirochetes were recovered in smears from the floor of peptic ulcers by Pewny[27] and identified in the walls by Lehner.[28] These were indubitably saprophytic spirochetes and since, as contended, spirochetes from the mouth cannot be readily distinguished morphologically from Spirochaetae pallidae, it is difficult to accept Warthin's assumption as proved. It is a noteworthy fact that in the only case of Warthin's in which any data were offered, the Wassermann reaction was found negative. When a lesion containing demonstrable spirochetes "in numbers" exists, a negative Wassermann reaction, it seems, would require investigation of the nature of the organisms present.

Some time ago I submitted for publication in one of the recognized journals an article on syphilis of the stomach which included two cases with classic anatomic findings. The manuscript was returned by the editor with the statement that in his opinion the frequent publication of "probable" cases did not greatly advance the subject. He wrote that he would be glad to accept any reports in which spirochetes had been demonstrated, and specified that a certain prominent authority on syphilis be persuaded to aid in the search. Following this suggestion, when the next case of syphilis of the stomach presented itself, I mailed the material to the investigator recommended, who kindly consented to examine it. He reported that the histologic appearance was characteristic of syphilis and that Spirochaetae pallidae were demonstrable in the section; the slide containing the organisms, with their location indicated, was returned to me. For reasons to be given later, the investigator's diagnosis was not accepted as final, since the spirochetes present were morphologically identical with those seen in nonsyphilitic stomachs. The essential available facts in connection with the case are here submitted for analysis.

REPORT OF A CASE

History.—A colored man, Oliver C., 22 years of age, entered the Cook County Hospital on Jan. 11, 1930, with the tentative diagnosis of obstructive ulcer. He related that he was first troubled nine months before entrance, when he noted a sense of epigastric fulness following meals. This at times was associated with

26. Brams, W. A.: Ueber das Ulcus syphiliticum multiforme ventriculi, Arch. f. Verdauungskr. **27**:375, 1921.

27. Pewny, W.: Spirochäten bei Ulcus ventriculi, Wien. med. Wchnschr. **70**: 1925 (Nov. 6) 1920.

28. Lehner: Ueber das Vorkommen von Spirillen im menschlichen Magen, Wien. klin. Wchnschr. **40**:957, 1927.

heart-burn. In a short while, actual pain supervened, occurring as a rule but once a day. The pain was epigastric and cramplike.

The patient's symptoms gradually increased in intensity until one month previous to admission, when a decided aggravation took place. The epigastric pain now occurred following every meal, being noted from fifteen minutes to one hour after eating. In the last two weeks of the illness the pain radiated around the right side to the middle of the back. Vomiting appeared almost simultaneously with the occurrence of postprandial pain. The vomiting became more and more frequent, and at the end of the two weeks the patient was unable to eat without subsequent emesis. The vomitus had the appearance of coffee-grounds.

The remainder of the history yielded only a few pertinent facts. The stools during the last few days of the patient's illness were tarry. The appetite was poor. During the month prior to entrance the patient estimated that he lost 25 pounds (11.3 Kg.). The loss of strength was quite profound. The patient acknowledged two gonorrheal infections, but denied syphilis. The family history suggested nothing indicative of syphilis.

Examination.—The patient appeared listless and showed evidence of loss of weight and pallor. A tumor mass was not palpated. From the laboratory standpoint it was determined that the first stool was tarry, but that the amount of blood rapidly decreased until merely occult blood remained. The material vomited the day of admission contained altered blood. A subsequent Ewald test meal yielded 195 cc. of poorly digested contents with 12 degrees free and 52 degrees combined acidity. The Wassermann and Kahn tests were 4 plus. A roentgenogram on January 22 was read by Dr. C. H. Warfield as follows: There was an irregular, annular constriction of the middle of the pars pylorica, which produced only moderate obstruction. Bordering on the lesser curvature, just proximal to the cylindric narrowing, there was a filling defect about which the rugous markings were lost. Carcinoma and syphilis were to be considered.

Course.—When the patient entered the ward, treatment for bleeding peptic ulcer was instituted. The positive report on the routine Wassermann test led to the suspicion of syphilis of the stomach, and antisyphilitic therapy (neoarsphenamine) was instituted two days after admission. Although the vomiting subsided to a great extent, the patient continued to complain of pain afer eating and on that account greatly curtailed his food intake. The attending physician to whom the patient was assigned considered the response to the two and a half weeks of antisyphilitic treatment too poor to support the diagnosis of syphilis of the stomach. He considered carcinoma more likely, and therefore recommended surgical intervention.

Operation.—Laparotomy undertaken on January 30 disclosed the pyloric portion of the stomach to be infiltrated by a relatively soft, elastic mass, which lacked the firmness and circumscription of a tumor. The encroachment on the lumen was only moderate. The perigastric glands were only slightly enlarged, pink and soft. There were no evidences of active or healed gummas detected in the examination of the liver. Because of the fear of carcinoma, gastric resection was performed. The patient withstood the immediate effects of the operation quite well. Beginning, however, with the third postoperative day his condition became worse. It was soon apparent that peritonitis had supervened. He died on February 5, six days after operation.

The postmortem examination was made by Dr. R. H. Jaffé, whose anatomic diagnosis reads: diffuse fibrinopurulent peritonitis; recent gastric resection and posterior gastro-entero-anastomosis with suppuration about the sutures; bilateral serofibrinous pleuritis with slight compression of the lower lobes; fatty

degeneration of the liver; parenchymatous degeneration of the myocardium and kidneys; infectious softening of the spleen; focal syphilitic aortitis in the region of the arch and above the aortic valve; an encapsulated tuberculous lesion in the left lower pulmonary lobe; circumscribed pyelonephritic atrophy of the left kidney; marked emaciation.

Surgical Specimen.—Gross Description: The unopened resected distal third of the stomach measured 7.2 and 11.5 cm. along the lesser and greater curvatures respectively. The specimen had roughly the shape of a dumbbell, owing to slight narrowing of its midportion over an area which measured 3 cm. Corresponding more or less to the extent of the cylindric constriction the serosa appeared white and fibrous. The differences between the apparently normal and abnormal portions, as determined by palpation, were far from striking. The narrowed area was felt to be thickened, but was only slightly increased in consistency and relatively supple. The pliability was in sharp contrast to the character of the infiltrate encountered in carcinoma with a similar distribution. The thickened area passed insensibly into the adjoining normal tissue. The opened specimen demonstrated that the moderate narrowing of the prepyloric region noted in the external examination was exaggerated by encroachment on the lumen of the thickened gastric wall. The area of maximum thickening, which was about the size of a silver dollar, was located on the anterior wall near the lesser curvature. From here the thickness of the wall diminished in passing radially. At the summit of the area of increased thickness there was a superficial ulcer with irregular, serpiginous margins. The maximum and minimum diameters measured 4.5 and 3.3 cm. respectively. The edges of the ulcer were neither raised nor undermined. The floor was covered with a grayish-brown, lardaceous, slightly adherent membrane. The remainder of the gastric lining, except for a little thickening, was unchanged. A cross-section of the wall in the region of the ulcer showed that the base of the latter was considerably above the level of the normal mucous membrane. The individual coats in the region of maximum thickness were adherent, but could be readily identified. The submucosa was represented by a relatively narrow layer of white, homogeneous tissue from which septums extended into the muscularis propria in lattice-like arrangement. The serous coat was greatly thickened, constituting from one-half to two-thirds the thickness of the gastric wall. It was composed of homogeneous, white tissue of elastic consistency.

Microscopic Description: The most pronounced changes were observed in sections taken in and about the region of the serpiginous ulcer which corresponded to the area of maximum thickness of the gastric wall. In passing centrifugally the histologic alterations became less and less prominent, leading gradually to relatively normal-appearing structures. The following description of a section taken from a margin of the ulcer to include the entire thickness of the stomach is quite representative (fig. 4).

Under very low magnification, the wall at one edge of the section was found to be increased to about three times the normal thickness, gradually tapering down in passing to the opposite end, to approach the thickness of the average stomach. In the thin portion the mucosa presented a relatively normal appearance except for an increased cellularity of the tunica propria. In approaching the margin of the ulcer the round and plasma cells in the interglandular tissue became more and more numerous and associated with an unusual number of prominent lymphoid follicles. As the wall became thicker the mucosa was displaced obliquely upward, until a point was reached at which the gastric lining was absent. The floor of the defect, however, continued for a short distance to pass obliquely upward, so that at no point was the normal mucosa above the level of the base of the ulcer.

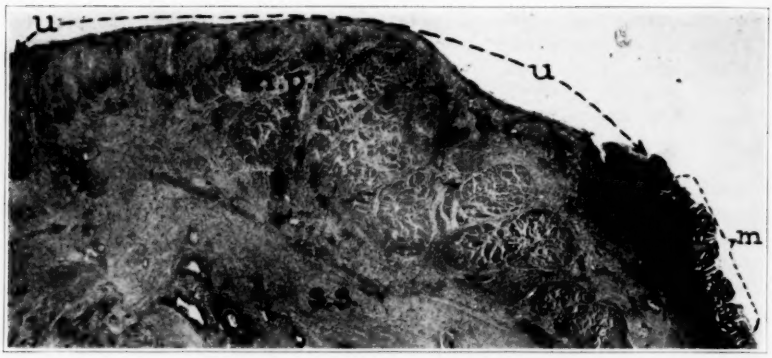


Fig. 4.—A cross-section of the wall of the stomach at the junction of the intact mucosa (*m*) and margin of the ulcer (*u*). At the periphery of the ulcer the floor is formed by submucosa (*s*); toward the center it is formed by muscularis propria (*m.p.*). The thickening of the gastric wall is due mainly to an increase in the subserosa (*s.s.*). The base of the ulcer is at a higher level than the intact mucosa. Obtained from the same specimen as the tissue shown in figure 5 (see report of case).

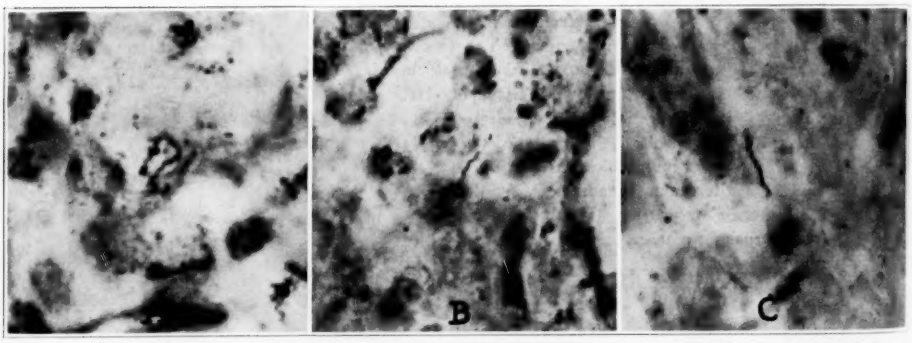


Fig. 5.—The material from which these photomicrographs were made was prepared and examined by an authority on the subject who made the diagnosis of syphilis from the histology and also from the morphology of the spirochetes demonstrated (see report of case). The three organisms pictured were found in separate fields. The spirochete which bore the closest resemblance to Spirochaeta pallida is shown in *A*. Most of the spirochetes encountered were of the types illustrated in *B* and *C*. The spirochete in *B* was actually twice as long as the photomicrograph indicates, since only one-half is included in the focus.

The muscularis mucosa showed moderate thickening due to an increase in muscle elements and infiltrations of round and plasma cells. It became lost after reaching the margin of the ulcer. The submucosa was also the seat of thickening due mainly to the presence of an increased and edematous connective tissue. Focal accumulations of cells, mainly round and to a lesser degree plasma cells, were scattered throughout this layer. In places these cells assumed a perivascular arrangement, but did not invade the vessel walls. In fact, the changes in the blood vessels themselves were exceedingly mild. In approaching the margin of the ulcer the cellular infiltrates became more numerous and larger, finally coalescing to form a solid wall. The submucosa, soon after entering the ulcer, constituted its floor and within a short space became destroyed.

The muscularis propria was invaded by connective tissue septums, which appeared to arise from the overlying and underlying layers. There were also accumulations of cells similar to those seen in the submucosa. The changes were most prominent in the ulcerated region, especially in that part in which the submucous layer was absent and the muscularis formed the base of the ulcer. Here the muscle bundles were infiltrated and the individual fibers appeared atrophic and stained poorly.

The serosa exhibited a prodigious thickening, constituting approximately one half of the total thickness of the gastric wall. The maximum increase was found underlying the area of ulceration. The histologic changes were similar to those found in the submucosa except that the fibrous tissue in the serosa was less dense.

The ulcer had a uniform base which resembled closely that of a peptic ulcer. The surface of the defect was covered by a dark, granular débris beneath which there was a zone of fibrinoid necrosis. Subjacent to this layer there was a young granulation tissue densely infiltrated by numerous round cells and lesser numbers of plasma, leukocytic and histiocytic cells. Underlying the layer of young granulation tissue was one which was poorer in cells and richer in collagen fibers. Successively the mucosa, muscularis mucosae, submucosa and superficial portions of the muscularis propria became destroyed. In no area did the base of the ulcer extend beyond the muscular coat.

Bacterioscopic and Biologic Examination.—Macerated preparations of gastric wall taken from the region of maximum involvement immediately after operation and examined with dark-field illumination failed to demonstrate the presence of Spirochaeta pallida. Inoculation of a saline suspension of the macerated tissue into the testicles of rabbits failed to produce signs of a scrotal chancre. Material taken from the same region which included the ulcer was fixed in a diluted solution of formaldehyde U. S. P. (1:10). Some blocks were retained and examined for tubercle bacilli, with negative results. Other blocks, together with pertinent data, were sent to the investigator previously referred to, with the request that he examine the tissue for Spirochaetae pallidae. His report read: "Positive for Spirochaetae pallidae. Typical spirochetes are rare. Atypical forms are more numerous, but are still uncommon. Granular and ring stages are common. The typical spirochetes are found only in the zone bordering the necrotic tissue of the ulcer. Histology characteristic of syphilis."

COMMENT

The location of those spirochetes considered most typical by the authority consulted was indicated by a ring of ink on a slide which he returned to me. The organism in this preparation which, in the opinion of the disinterested observers (Drs. R. H. Jaffé and I. Pilot),

resembled classic Spirochaeta pallida most closely is pictured in figure 5 *A*. The more frequent type encountered is illustrated in figure 5 *B* and *C*. Neither I nor my associates in pathology and bacteriology could distinguish the spirochetes found within the circle from those seen in necrotic lesions of nonsyphilitic origin. One is led to believe that the spirochetes found in the section and considered of the pallida type by the investigator were more probably saprophytic than pathogenic. As stated by him in his letter and indicated by him in the section, the "typical" spirochetes were found only in the zone bordering the necrotic tissue of the ulcer. In the foregoing description it was pointed out that saprophytic spirochetes morphologically resembling the syphilitic type are frequently located in and border on necrotic lesions of the stomach. It was stated, furthermore, that these spirochetes were generally accompanied by fusiform bacilli together with other microorganisms. In the consultant's section fusiform bacilli could be found with relative ease and, in fact, served as a guide in the search for spirochetes. By far most of the spirochetes found were of the type illustrated in figure 5 *B* and *C* and were distinctly different from the classic ones, as indicated by the consultant's statement, viz.: "Typical spirochetes are rare. Atypical forms are more numerous but are still uncommon." These "atypical" Spirochaetae pallidae appear morphologically to be identical with certain varieties of mouth spirochetes found in nonspecific necrosis of gastric as well as other tissues.

Assuming the consultant's bacteriologic diagnosis of Spirochaeta pallida to be doubtful, the question naturally arises as to the evidence on which the diagnosis of gastric syphilis is founded. The histologic picture, although compatible with the diagnosis of syphilis, is not distinctive of this disease. In fact, the changes in this case are less characteristic of syphilis than those in any of the other cases that I have reported. In all previous instances which were studied microscopically the vascular changes were at least in a measure typical of syphilis. In the stomach herein described neither the arteries nor the veins were the seat of any noteworthy degree of inflammation. It is not unlikely that the antisyphilitic therapy modified to some extent the histology of the lesion. The diagnosis is based in this instance on collective evidence derived mainly from clinical data: the age of the patient (22 years), the progressive course, the hypochlorhydria, the roentgen observation of an irregular, annular deformity, situated proximal to and not invading the pylorus, and the positive Wassermann reaction. Further support is adduced from the therapeutic response which, although not striking, was sufficient to conclude that the patient was greatly benefited by the antisyphilitic treatment. The gross description of the lesion is quite characteristic of syphilis. The typical features

include a relatively soft, indefinitely outlined infiltrate in the thickest portion of which is a superficial, serpiginous ulcer of irregular form. The absence of a noteworthy degree of lymphadenopathy and the lack of microscopic evidence of carcinoma are of negative value in the diagnosis. Finally the autoptic demonstration of a syphilitic aortitis and no other disease or lesion to explain the gastric involvement lends additional support to the diagnosis.

It is thus seen that what might have been recorded as a case of "proved" gastric syphilis based on the demonstration of spirochetes was actually one of presumptive or perhaps questionable syphilis. The diagnosis rests on clinical, laboratory, therapeutic and macroscopic anatomic observations. The bacterioscopic and histologic examinations yielded nothing of positive value in arriving at the diagnosis. It is quite possible that the gastric involvement represented a nonsyphilitic granuloma in a syphilitic patient rather than a true syphilitic lesion. In either event from the clinical standpoint it would have been to the patient's advantage to have treated him on the supposition that he was suffering from a syphilitic disease of the stomach. Whatever the conclusions of the morbid anatomists may be, the fact remains that, clinically, patients who present the foregoing syndrome are best treated for gastric syphilis. Obviously, all precautions against mistaking carcinoma for syphilis must be observed. In doubtful cases operation is indicated. The differentiation can generally be made with relative ease, particularly with the aid of a frozen section, which is of value in excluding malignancy.

NOTE.—Since this article was submitted for publication a report appeared by Harris and Morgan dealing with the demonstration of spirochetes from a syphilitic stomach by means of inoculation of animals.[29] The description of the gross and histologic characteristics of the resected specimen is too brief to admit of any opinion. The spiral forms pictured in a photomicrograph of a section stained by the Levaditi method do not resemble spirochetes and, as the authors themselves state, "could not be identified as Spirochaeta pallida." However, inoculation of a tissue suspension of material from the gastric lesion and also from a regional lymph gland into four rabbits resulted in testicular syphilomas in two and a scrotal chancre in one of these two. Dark-field examination of scrapings from the lesions revealed "Spirochaeta pallida in countless numbers and typical in form." Repeated transfer of the spirochetes to other rabbits resulted, according to the authors, in the production of characteristic local and metastatic lesions of experimental syphilis.

In a discussion of gastric syphilis before the Section on Gastro-Enterology at the eighty-first annual session of the American Medical Association in June, 1930, I emphasized the difficulty in differentiating certain types of spirochetes in Levaditi preparations. I further stated: "A hanging drop preparation is more favorable for identification of spirochetes of syphilis, and rabbit inoculation, when positive,

29. Harris, S., and Morgan, H. J.: The Isolation of Spirochaeta Pallida from the Lesion of Gastric Syphilis, J. A. M. A. **99**:1405 (Oct. 22) 1932.

most conclusive."[30] It should be borne in mind, however, that although animal inoculation offers more conclusive evidence than other methods of differentiating spirochetes, the experimental lesions and the organisms obtained therefrom are by no means unmistakable. Rabbit spirochetosis, a spontaneous venereal disease of rabbits, constitutes a potential source of error in that the etiologic organism, Spirochaeta cuniculi, is practically indistinguishable from Spirochaeta pallida (Noguchi[31]). A number of reliable distinguishing features, clinical, serologic and anatomic, between rabbit spirochetosis and experimental syphilis are recognized by many authorities; nevertheless dissenting views are not lacking.[32]

The observation by Neumann[33] of the spontaneous appearance in a rabbit of spirochetes of the pallida type adds further to the doubt expressed by several authors regarding the value of the rabbit in the recognition of syphilis in human beings. Of particular interest is the report of Worms,[34] who inoculated a rabbit with material from the mouth of a nonsyphilitic man. The rabbit developed lesions which contained spirochetes indistinguishable from Spirochaeta pallida. Attempts to inoculate other rabbits from the experimental lesions were uniformly successful. On account of the possibility of error in connection with animal inoculation all available evidence should be gathered and recorded in order to establish proof when the diagnosis of syphilis of the stomach is made. Although the work of Harris and Morgan is quite convincing, confirmation by others is nevertheless desirable.

---

30. Singer, H. A., in Discussion on Gastric Syphilis, J. A. M. A. **96**:186 (Jan. 17) 1931.

31. Noguchi,[15] p. 478.

32. Sobernheim, G.: Syphilisspirochäte, in Kolle, W.; Kraus, R., and Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1930, vol. 7, pt. 1, p. 107.

33. Neumann, F.: Ueber das spontane auftreten von Spirochäten des pallidatyps bei einem Nichtsyphilitischen, isolierten Kaninchen, Klin. Wchnschr. **2**:256 (Feb. 5) 1923.

34. Worms, W.: Bemerkungen zur Arbeit von Dr. F. Neumann, Klin. Wchnschr. **2**:836 (April 30) 1923.

EXPERIMENTAL CORONARY OCCLUSION

INADEQUACY OF THE THREE CONVENTIONAL LEADS FOR RECORDING CHARACTERISTIC ACTION CURRENT CHANGES IN CERTAIN SECTIONS OF THE MYOCARDIUM; AN ELECTROCARDIOGRAPHIC STUDY

FRANCIS CLARK WOOD, M.D.
AND
CHARLES C. WOLFERTH, M.D.
WITH THE TECHNICAL ASSISTANCE OF MARY M. LIVEZEY, A.B.
PHILADELPHIA

It has been known since the original observations of Smith [1] and Pardee [2] that in some instances an acute myocardial infarction causes a characteristic change in the ventricular complex of the electrocardiogram. In certain other instances of infarction, however, definite electrocardiographic evidence of the presence of the infarct has not been obtained. The reason for this apparent limitation of the electrocardiographic method in both clinical and experimental studies has not been clearly understood.[3] The observations to be reported here have a bearing on this problem.

EXPERIMENTS

In our earlier studies the following technic was employed: Dogs were subjected to iso-amyl-ethyl-barbituric acid anesthesia. A cannula was placed in the trachea and connected with the ordinary respiratory pump. The chest was opened along the sternum. The pericardium was opened longitudinally. Its edges were sewed to the lateral wall of the chest, making a hammock to hold the heart in position. The coronary arteries were dissected free; threads were passed beneath

Submitted for publication, April 14, 1932.
From the Edward B. Robinette Foundation, Hospital of the University of Pennsylvania.

1. Smith, F. M.: The Ligation of Coronary Arteries with Electrocardiographic Study, Arch. Int. Med. **22**:8 (July) 1918.

2. Pardee, H. E. B.: An Electrocardiographic Sign of Coronary Artery Obstruction, Arch. Int. Med. **26**:244 (Aug.) 1920.

3. (*a*) Wood, F. C., and Wolferth, C. C.: Angina Pectoris: The Clinical and Electrocardiographic Phenomena of the Attack and Their Comparison with the Effects of Experimental Temporary Coronary Occlusion, Arch. Int. Med. **47**: 339 (March) 1931. (*b*) Feil, H. S.; Katz, L. N.; Moore, R. A., and Scott, R. W.: The Electrocardiographic Changes in Myocardial Ischemia, Am. Heart J. **6**:522 (April) 1931.

them to facilitate subsequent manipulations. Coronary occlusion was produced by means of bulldog clamps. Electrocardiograms were taken with the three conventional limb leads. The accompanying table shows the number of animals employed, and indicates the numbers of the various experiments carried out.

We found,[3a] as did other observers,[3b] that occlusion of the anterior descending branch of the left coronary artery produced little or no change in the electrocardiogram, despite a marked alteration of the appearance and action of the heart. Obstruction of the right coronary artery likewise caused practically no change in the ventricular complex. However, when the posterior circumflex branch of the left coronary artery or one of its large descending branches was occluded, a definite

Summary of Experimental Procedures

	Series 1*	Series 2†	Series 3‡	Series 4§
Number of dogs used	10	6	10	8
Number of experiments in which the left anterior descending artery was clamped	34	15	31	29
Branch of left anterior descending artery clamped	6	15	1	4
Right coronary artery clamped	24	9	20	10
Left posterior circumflex artery clamped	48	10	6	20
Branch of left posterior circumflex artery clamped	20	..	2	6
Vena cava alone occluded	12	..	24	..
Vena cava plus a coronary artery	22	..	8	..
Coronary sinus alone occluded	4	..	..	..
Coronary sinus plus a coronary artery	6	..	..	..
Anoxemia of whole heart	9	..	..	..
Anoxemia plus a coronary artery	5	..	..	..

* Series 1 includes all those experiments done with the chest and pericardium open widely.
† Series 2 shows the number of experiments with electrograms. All these dogs were used in series 3 also.
‡ Series 3 shows the number of experiments done with the method allowing improved conduction from the anterior surface of the heart to the electrodes.
§ Series 4 is composed of the experiments in which chest leads were used.

and striking elevation of the RS-T interval appeared [3a] (fig. 1). It was found, moreover, that each time this artery was clamped, the same type of change appeared in the electrocardiogram.[4]

In the dog, therefore, we are confronted with a situation analogous to that existing in man. When one coronary artery is occluded, a characteristic change appears in the RS-T interval of the electrocardiogram. When another coronary artery is obstructed, no such change develops.

Further experimentation elicited the following facts:

1. The appearance time of the elevation of the RS-T interval, following occlusion of the left posterior circumflex artery, is always less

4. In a previous publication,[3a] two figures were shown in which a deep inversion of the T wave appeared after a descending branch of the left posterior circumflex artery had been clamped. Subsequent experiments have shown that this is sometimes an intermediate step during the development or during the disappearance of the typical elevation of the RS-T interval.

than two minutes (fig. 2). It is influenced somewhat by the heart rate; the more rapid the rate, the more quickly the changes tend to appear. The data now at hand do not support our earlier impressions [3a] that previous damage to the heart definitely shortens this period.

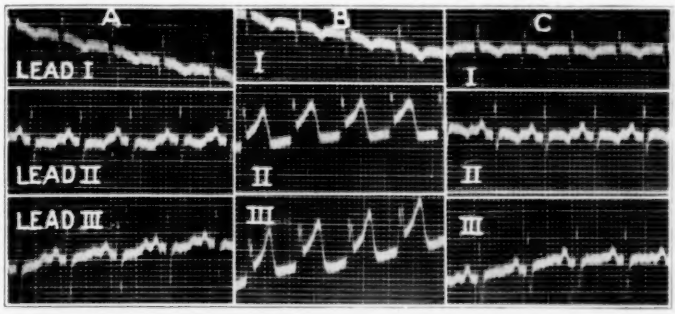


Fig. 1.—Electrocardiographic changes after occlusion of the posterior circumflex branch of the left coronary artery. *A*, control, before the occlusion. *B*, one minute after occlusion of the artery. The vein was not obstructed. A definite elevation of the RS-T interval is seen in leads II and III. The clamp was then immediately removed. *C*, four minutes after removal of the clamp, showing a disappearance of the electrocardiographic change.

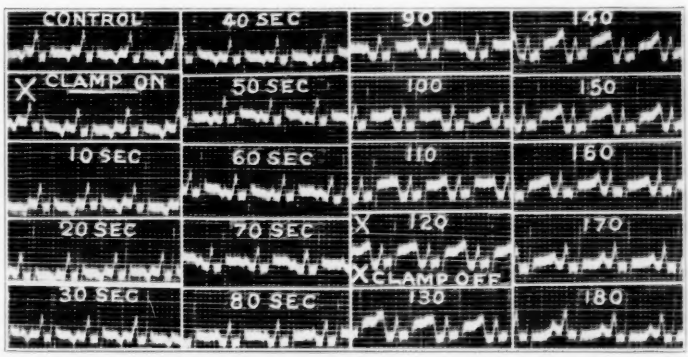


Fig. 2.—The rate of appearance and disappearance of the elevation of the RS-T interval after occlusion of the posterior circumflex branch of the left coronary artery. Tracings were taken in lead II every ten seconds. The clamp was removed after one hundred and twenty seconds. A definite elevation of the RS-T interval is seen in ninety seconds. It disappeared sixty seconds after removal of the clamp, although changes in the T wave are still present.

2. The appearance of the elevation of the RS-T interval is not dependent on the simultaneous obstruction of accompanying veins, as

suggested by Feil, Katz, Moore and Scott.[3b] Occlusion of the accompanying veins does not even tend to accelerate the development of this change. Furthermore, the coronary sinus can be clamped for at least five minutes without producing an RS-T elevation, despite a marked congestion of the coronary veins.[5] At the end of this period, if the left posterior circumflex artery is clamped without removing the coronary sinus clamp, the elevation of the RS-T interval does not appear more readily than when the artery alone is occluded.

3. The appearance or the nonappearance of the typical deviation of the RS-T interval in the first series of experiments did not seem to be entirely dependent on the size of the infarct.[6] When both the right coronary artery and the anterior descending branch of the left coronary artery are occluded simultaneously and the entire anterior surface of the heart is deprived of its arterial blood supply, no definite

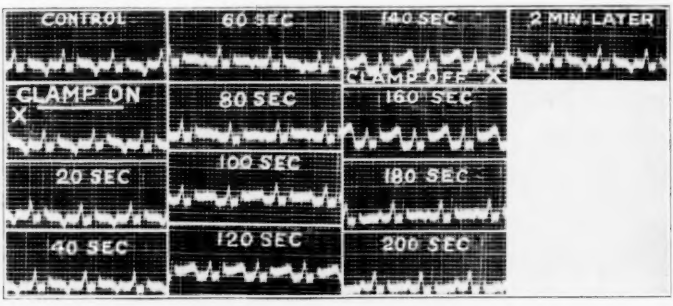


Fig. 3.—Elevation of the RS-T interval produced by clamping of one of the descending branches of the left posterior circumflex coronary artery. Tracings were taken in lead II every twenty seconds. At one hundred seconds, the change was definitely present. It had practically disappeared sixty seconds after the removal of the clamp.

change appears in the electrocardiogram. However, when one of the descending branches of the left posterior circumflex artery is clamped and a much smaller area of the myocardium is infarcted, elevation of the RS-T interval appears rapidly (fig. 3).

5. J. Cohnheim and A. von Schulthess Rechberg (Ueber die Folgen der Kranzarterien verschliessung für das Herz, Virchows Arch. f. path. Anat. **85**:503, 1881) observed that the heart would continue to beat for an indefinite time (over thirty minutes) after ligation of the coronary sinus, without apparent impairment of its power. They also observed that ligation of the accompanying veins with a coronary artery did not accelerate the death of the animal.

6. For want of a more accurate and concise word, the term "infarct" is used in this article to signify a section of the myocardium the arterial blood supply of which has been temporarily interrupted. "Potential infarct" would be more strictly correct.

Therefore, under the conditions of these experiments, the appearance or the nonappearance of a deviation of the RS-T interval from the iso-electric line after occlusion of a coronary artery seems to be dependent in some way on the position which the resulting infarct occupies in the heart. An anterior infarct causes no definite change in the electrocardiogram. On the other hand, a posterior infarct, even though smaller, causes a well defined elevation of the RS-T interval.

Two possible explanations for this phenomenon present themselves: (1) an anterior infarct does not cause a change in the action current of the heart, and (2) it produces a change in the action current, but this change is not recorded in the limb leads of the electrocardiogram.

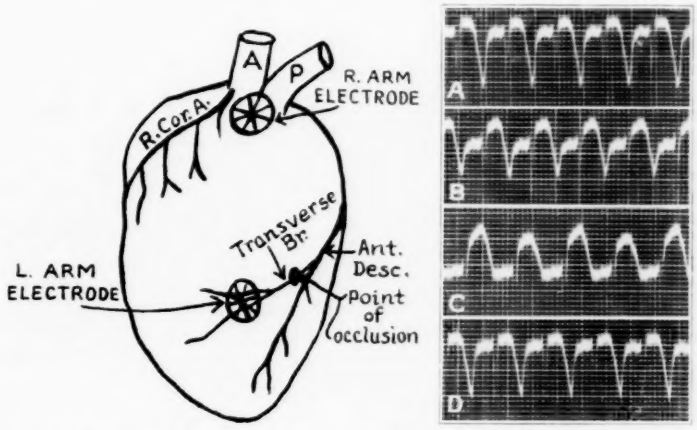


Fig. 4.—Occlusion of a small transverse branch of the anterior descending branch of the left coronary artery. Electrodes placed directly on the surface of the heart. The positions of the electrodes and the point of occlusion are indicated in the diagram. Since the left arm electrode was on the infarcted area, an elevation of the RS-T interval of the electrogram occurred. It disappeared completely within four minutes after the clamp was removed. *A*, control. *B*, tracing taken one minute after occlusion of the transverse branch of the left anterior descending coronary artery. *C*, tracing taken one minute after *B*; clamp still in place. The occlusion was then released. *D*, four minutes after removal of the clamp.

In order to test the first hypothesis, electrodes[7] were placed directly on the surface of the heart, and the various anterior arteries were clamped. It was found that a deviation of the RS-T interval will appear in the electrogram within two minutes after occlusion of either the right coronary artery or the anterior descending branch of the

7. The type of electrodes described by T. Lewis (The Mechanism and Graphic Registration of the Heart Beat, London, Shaw & Sons, Ltd., 1925) was used.

left coronary artery if one electrode is located on the infarcted area. Even small infarctions on the anterior surface of the heart cause changes in the RS-T interval if the electrodes are suitably placed (fig. 4). The direction of the deviation of the RS-T interval depends on which electrode is situated on the infarct. When the right and the left arm lead wires are used, an infarction under the right arm electrode produces a depression of the RS-T interval (fig. 5); an infarction under the left arm electrode produces an elevation of the RS-T interval (fig. 4). We do not mean to imply that changes in the RS-T interval fail to appear unless one of the electrodes is located directly on the area of infarction. If, for instance, the right arm electrode is

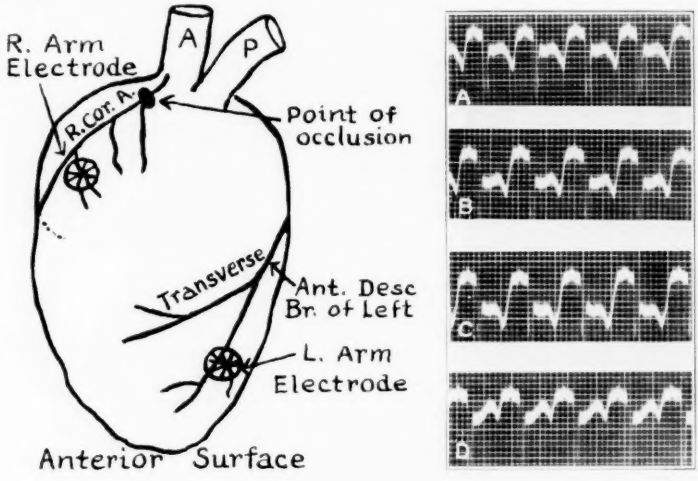


Fig. 5.—Electrogram resulting from occlusion of the right cornary artery. The positions of the electrodes and the point of occlusion are shown in the diagram. A slight depression of the RS-T interval was present in the control. This may have been due to previous damage to the circulation in this area. Since the right arm electrode was on the infarcted area, a depression of the RS-T interval was recorded. Four minutes after the removal of the clamp, the tracing had practically returned to its previous state. *A*, control. *B*, tracing taken one minute after occlusion of the right coronary artery. *C*, tracing taken one minute after *B*; clamp still in place. The clamp was then removed. *D*, four minutes after removal of the clamp.

placed on the lower anterior surface of the heart and the left arm electrode is placed on the left leg, a posterior infarct will produce an elevation of the RS-T interval in this lead, i. e., a deviation in a direction opposite to that produced by an anterior infarct.

It appears, therefore, that whenever infarction of an appreciable section of the surface of a dog's heart occurs, a change rapidly takes

place in the action current of the infarcted area, and within two minutes a deviation of the RS-T interval from the iso-electric line is recordable from this area. Quite evidently, then, the nonappearance

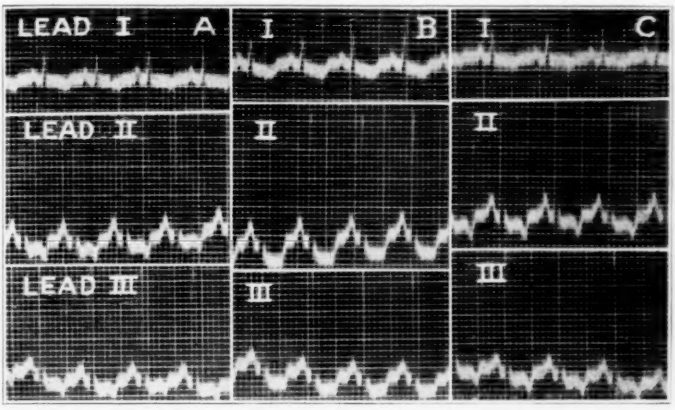


Fig. 6.—Occlusion of the right coronary artery; conduction from the front of the heart improved. *A*, control. *B*, three minutes after the occlusion, showing a depression of the RS-T interval in leads II and III and a deeper inversion of T_3. The clamp was then removed. *C*, five minutes after the removal of the clamp.

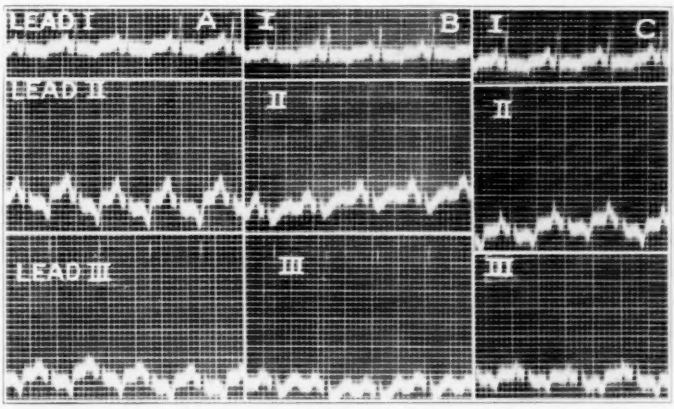


Fig. 7.—Occlusion of the anterior descending branch of the left coronary artery; conduction from the front of the heart improved. *A*, control. *B*, one and a half minutes after the artery was occluded. T_2 and T_3 have become upright. The clamp was then removed. *C*, four minutes after removal of the clamp.

of changes in the RS-T interval following anterior infarction in our earlier experiments was due merely to a failure to record an electrical

change which was taking place. It was not due to the fact that a change in the action current had failed to develop.

The next step, therefore, was to determine the cause of our previous failure to record this change in the action current after the anterior arteries had been occluded. On reconsideration of our technic, it occurred to us that the entire anterior surface of the heart had been exposed to the air; the posterior surface had been in intimate contact with the pericardium and the posterior mediastinal structures. It was thought that the failure to record electrocardiographic changes after anterior infarction might be dependent on inadequate electrical conduction from the anterior surface of the heart to the limbs. Conse-

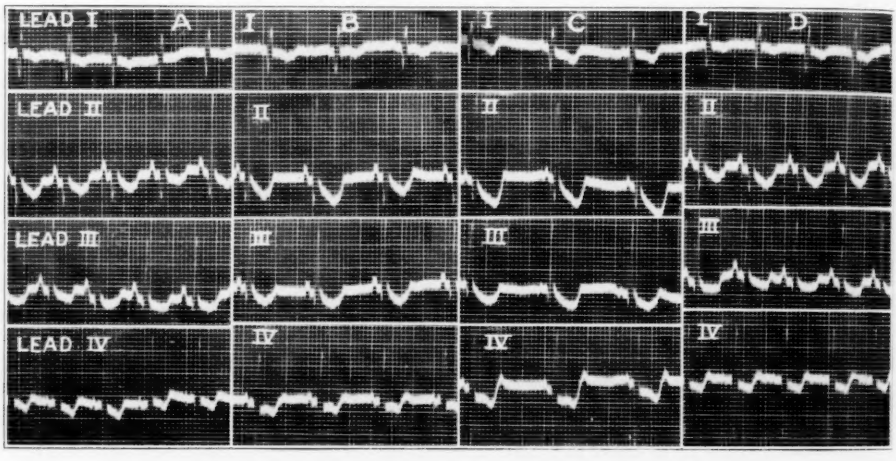


Fig. 8.—Occlusion of the right coronary artery. Four leads were used. Lead IV was taken from electrodes placed on the anterior and posterior surfaces of the wall of the chest. The anterior one was placed opposite the fourth, fifth and sixth ribs, immediately to the right of the sternum, and was connected to the right arm lead wire. The posterior one was placed opposite the anterior one, just to the left of the spine, and was connected to the left arm lead wire. *A*, control. *B*, tracing taken during the second minute after clamping of the right coronary artery. *C*, tracing taken during the fifth minute after the occlusion; the clamp was still in place. A depression of the T wave in lead I and of the RS-T interval in leads II, III and IV is seen. A slowing of the heart rate is apparent. The clamp was then removed. *D*, four minutes after removal of the clamp.

quently, in the next group of experiments the pericardium was not widely opened. The arteries were approached through small slits in this membrane, and its connections with the anterior wall of the chest and the diaphragm were left intact. With this technic it is possible to record certain changes in the electrocardiogram after occlusion of

the anterior arteries. These changes are specific for each of the two arteries. Occlusion of the right coronary artery regularly produces a depression of the T wave and the RS-T interval (fig. 6). Occlusion of the anterior descending branch of the left coronary artery changes the T wave from negative to positive (fig. 7). Certain of our tracings also show a slight slurring of the terminal portion of the downstroke of R.

These experiments show that specific changes can be produced in the electrocardiogram of the dog by clamping the right coronary artery and the anterior descending branch of the left coronary artery, as

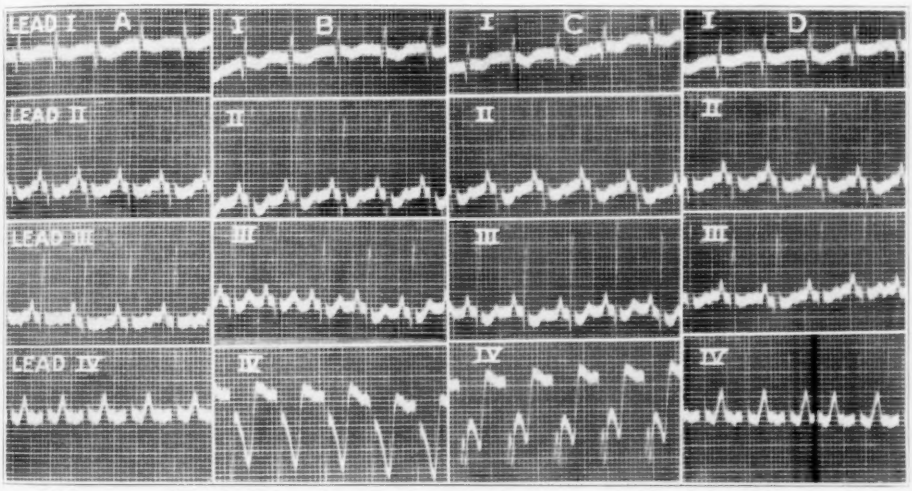


Fig. 9.—Occlusion of the anterior descending branch of the left coronary artery —four leads. Preparation made as for figure 8. *A*, control. *B*, tracing taken during the second minute after clamping of the artery. The T wave in leads II and III have become upright. The RS-T interval in lead IV is depressed. *C*, tracing taken during the third minute after clamping of the artery. T_2 and T_3 show no further change. The RS-T interval in lead IV is more deeply depressed. The clamp was then removed. *D*, tracing taken five minutes later, showing disappearance of the changes.

well as by clamping the left posterior circumflex. The results fall in line with the observations made in man by Barnes and Whitten.[8] Nevertheless, although these changes in the dog are specific for each artery, no deviation of the RS-T interval followed occlusion of the left anterior descending artery. Moreover, although failure of conduction from the

8. Barnes, A. R., and Whitten, M. B.: Study of the R-T Interval in Myocardial Infarction, Am. Heart J. **5**:142 (Dec.) 1929.

anterior surface of the heart was a factor in our experiments, it would not be likely to occur in man. Consequently, it could not account for a failure of development of electrocardiographic changes following acute coronary occlusion in human beings.

These considerations led to another set of experiments in which the position of the electrodes on the surface of the body was changed. In addition to the three conventional leads, another lead was used. The electrodes were placed directly on the anterior and posterior surfaces of the wall of the chest. The right arm lead wire was attached to the anterior electrode; the left arm lead wire was connected to the posterior one. Certain other alterations in technic were made. The animal was turned partly on the right side. The chest was opened

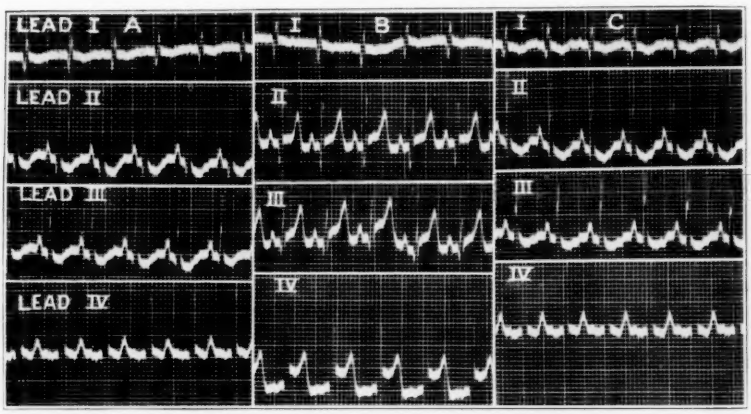


Fig. 10.—Occlusion of the posterior circumflex branch of the left coronary artery—four leads. *A*, control. *B*, tracings taken between forty-five and ninety seconds after occlusion of the artery. The typical elevation of the RS-T interval is seen, beginning in leads II and III, and well developed in lead IV. The clamp was then removed. *C*, four minutes later, showing disappearance of the changes.

on the left.[9] The heart was approached through as small an incision as possible. After isolation of the coronary arteries, the chest was filled with warm physiologic solution of sodium chloride in order to insure adequate conduction from all surfaces of the heart.

Figures 8, 9 and 10 show the results obtained with this technic by clamping the right coronary artery, the anterior descending branch

9. The right coronary artery was isolated through a preliminary incision on the right side; this incision was closed before we proceeded to the other side. By means of a thread placed under the right artery, this vessel could later be reached and clamped through the incision on the left side.

of the left coronary artery and the posterior circumflex branch of the left coronary artery, respectively. It is apparent that within two minutes after the occlusion of any one of these arteries, a change in the RS-T interval of the electrocardiogram appears in one or more of the four leads. In the case of the right and the left posterior circumflex arteries, this change appears in several leads. When the left anterior descending artery is occluded, a deviation of the RS-T interval appears only in the anteroposterior chest lead.

Thus, finally, the cause becomes apparent why we and other workers [3b] had previously failed to record deviations of the RS-T interval after occlusion of the anterior descending coronary artery. The change

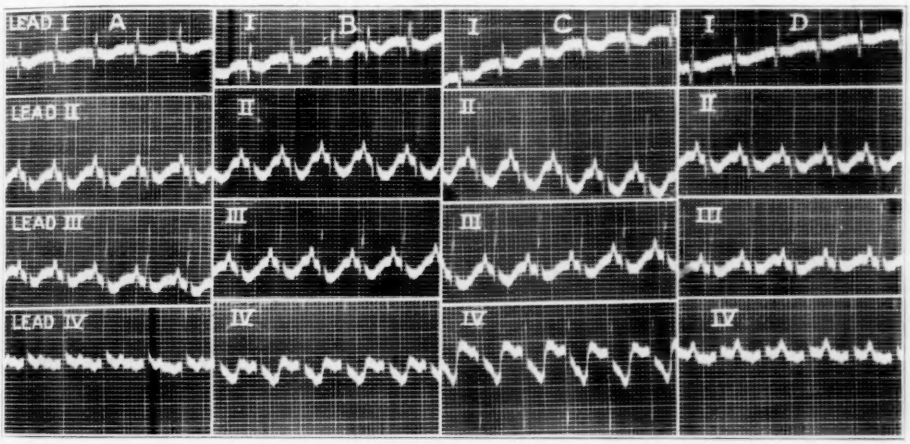


Fig. 11.—Occlusion of the transverse branch of the left anterior descending coronary artery—four leads. *A*, control. *B*, tracing taken during the second minute after clamping of the artery. T_2 and T_3 do not become upright, as when the main artery is clamped. T_4 and RS-T_4 are beginning to invert. *C*, tracing taken during the third minute after occlusion. T_2 and T_3 are the same as in *B*. The RS-T interval in lead IV is distinctly depressed. The clamp was then removed. *D*, five minutes later; the changes have disappeared.

in the action current had occurred each time the artery was clamped. All that was necessary to record it in the electrocardiogram was: first, satisfactory conduction from the anterior surface of the heart to the surface of the body, and second, a departure from the three conventional leads and the application of the electrodes to the front and the back of the wall of the chest.

The discovery of the latter fact led us to use an anteroposterior chest lead in the study of human coronary occlusion. In a previous

publication,[9a] a case of acute myocardial infarction was reported in which the chest lead showed a marked deviation of the RS-T interval from the iso-electric line when the conventional three leads showed no such phenomenon.

COMMENT

It is apparent, therefore, that infarction can occur, both in the dog and in man, in such a position in the heart that it will produce a deviation of the RS-T interval from the iso-electric line in an anteroposterior chest lead, but not in the three conventional leads. On the other hand, in some cases the routine electrocardiogram may show the deviation of the RS-T interval when the anteroposterior chest lead does not.[10]

We have not determined how large an infarct must be in order to produce a deviation of the RS-T interval which is recordable from the surface of the body. We do know, however, that occlusion of a relatively small branch of the left anterior descending coronary artery in the dog will produce such a change in the chest lead (fig. 11).

Einthoven and his co-workers,[11] Wilson [12] and Craib,[13] have pointed out the fundamental electrophysical laws which govern the contour of electrocardiograms recorded from various parts of the body. Consequently, a discussion of the factors that determine the appearance or the nonappearance of deviations of the RS-T intervals in various leads need not be undertaken in this article. Suffice it to say that it may be advisable to use three leads in addition to the conventional limb leads in the study of patients with coronary occlusion: (*a*) an anteroposterior chest lead, (*b*) a lead from the anterior surface of the chest to the left leg and (*c*) one from the posterior surface of the chest to the left leg. These six leads, three of which are situated in each of two planes perpendicular to each other, should serve to detect the majority of cardiac infarcts. Whether there are areas in the myocardium

9a. Wolferth, C. C., and Wood, F. C.: The Electrocardiographic Diagnosis of Coronary Occlusion by the Use of Chest Leads, Am. J. M. Sc. **183**:30 (Jan.) 1932.

10. Wolferth, C. C., and Wood, F. C.: Further Observations upon the Use of Chest Leads in the Electrocardiographic Study of Coronary Occlusion, M. Clin. North America **16**:161 (July) 1932.

11. Einthoven, W.; Fahr, G., and deWaart, A.: Ueber die Richtung und die manifeste Grösse der Potentialschwankungen im menschen Herzen und über den Einfluss der Herzschlage auf die Form des Elektrokardiogramms, Arch. f. d. ges. Physiol. **150**:275, 1913.

12. Wilson, F. N.: The Distribution of the Potential Differences Produced by the Heart Beat Within the Body and at Its Surfaces, Am. Heart J. **5**:599 (June) 1930.

13. Craib, W. H.: The Electrocardiogram, Medical Research Council, Special Report Series, no. 147, London, His Majesty's Stationery Office, 1930.

where infarction can occur without producing deviations of the RS-T interval in any of these leads, we do not know.

Our experiments on the dog and our observations on man [14] indicate the probability that chest leads may be of considerable help in the localization of myocardial infarcts.[8] When the electrodes are applied to the thoracic wall of a dog, as we have specified, the RS-T interval is depressed by an anterior infarct, whereas it is elevated by a posterior one. These results are similar to those obtained with leads placed directly on the heart (figs. 4 and 5). When the right arm electrode is over the infarcted area, the RS-T interval is depressed. When the left arm electrode is over the infarcted area, the RS-T interval is elevated. It is possible, therefore, that a fair degree of accuracy may be attainable in the localization of myocardial infarcts in man by noting which position of the electrodes on the chest gives a maximum deviation of the RS-T interval, and by observing the direction of this deviation.

In our early work with direct and semidirect leads (Wilson [12]) it was thought that the change in the action current produced by an infarct affected only the electrode which was placed directly on or over the lesion. However, as we have previously intimated, this is not the case. When the following three leads are used: (*a*) an antero-posterior chest lead, (*b*) a lead from the anterior surface of the chest to the left leg and (*c*) one from the posterior surface of the chest to the left leg, a posterior infarct may cause an elevation of the RS-T interval in (*a*) and (*b*) and no deviation of this interval from the iso-electric line in (*c*).

It must be emphasized here that the dog's heart differs from the human heart in certain important anatomic respects. Therefore, although certain general principles mentioned in this paper apply equally to both, certain specific results of our experiments are not necessarily transferable to man.

The interpretation of human tracings taken by chest leads is dependent on an adequate series of normal controls. Only a small beginning has been made in assembling such a series. When we know exactly what to expect in normal subjects, chest leads may be of considerable use in routine electrocardiography. Localized myocardial lesions of a chronic nature might well be present without producing any abnormalities in the conventional electrocardiogram. In certain cases it may be possible to discover such lesions by means of chest leads.

The question of the appearance time of the changes in the RS-T interval after coronary occlusion merits further discussion. Hurxthal [15]

14. Wolferth and Wood (footnotes 9a and 10).

15. Hurxthal, L. M.: The Appearance Time of T Wave Changes in the Electrocardiogram Following Acute Coronary Occlusion, Arch. Int. Med. **46**:657 (Oct.) 1930.

has investigated this problem in man. It is well known that a three lead electrocardiogram taken on the day of onset may show no change in the RS-T interval, and that this change may appear subsequently in a tracing taken hours or days later. This has given rise to an impression that the changes of the RS-T interval in coronary occlusion take hours or days to develop. However, when a dog's coronary artery is clamped, the deviation of the RS-T interval dependent on that occlusion appears within two minutes. It is not readily conceivable, therefore, that a similar change in the action current takes much longer to develop in man. Failure in the past to record this change promptly after the onset of an attack of coronary occlusion may have been due to one of two causes: (1) the infarct was too small to produce deviations of the RS-T interval which were recordable at the surface of the body, or (2) the lesion was situated in a part of the heart where infarction does not produce changes in the RS-T interval in the conventional limb leads.[16] Subsequent development of deviations of the RS-T interval may be due to an extension of the thrombosis into other coronary arteries, thereby either enlarging the lesion or extending it into areas which will affect the limb leads. Occasionally, the late appearance of changes in the RS-T interval may be due to the fact that the original attack is caused by an incomplete arterial obstruction, giving rise to pain, but not to changes in the action current. Later, when the occlusion becomes complete, the change in the action current appears. There is no evidence that the change in the action current and the pain appear simultaneously, when a disturbance occurs in the arterial circulation of the heart.

Feil, Katz, Moore and Scott [3b] ligated the left anterior descending coronary artery. No change occurred in the RS-T segment of the electrocardiogram. After a certain number of minutes had elapsed, the inferior vena cava was clamped. An elevation of the RS-T interval appeared; it disappeared when the vena cava was released. Their conclusion was "that RS-T deviation is a manifestation of myocardial ischaemia, in the production of which coronary occlusion is one factor." It appears to have been their impression that coronary occlusion alone will not cause a deviation of the RS-T interval, and that, in addition, a reduction of blood pressure is necessary to bring about this change in the electrocardiogram. Our experiments (fig. 9) show that the data on which this conclusion is based are inadequate; changes in the RS-T interval are recordable in experiments of the type performed by these workers, provided chest leads are employed and satisfactory conduction

16. An instance of this second type has been published [9] in which the antero-posterior part of the chest had alone showed the change.

is obtained from all surfaces of the heart. We have not recorded the blood pressure in our animals. Consequently, our data do not refute their stated conclusion. It is clear, however, that no additional impairment of the coronary circulation or of the general circulation is necessary for the production of deviations of the RS-T interval beyond that produced by occlusion of a coronary artery. The experimental results of Feil and his co-workers might be explained if a reduction of blood pressure could be shown to cause enlargement of an already existing infarct. However, further work is necessary to substantiate this speculation.

Our observations on the results of clamping the inferior vena cava are difficult to interpret. Occlusion of this vessel alone depresses the RS-T interval of the electrocardiogram, reduces the size of the heart and slows its rate markedly. When the vena cava is clamped five minutes before, or simultaneously with, the left posterior circumflex artery, the appearance of the elevation of the RS-T interval seems to be retarded slightly. This may be dependent on the slowed heart rate. Further experimentation is necessary to determine the electrocardiographic results of clamping the vena cava, with and without coronary occlusion.

Gruber and Kountz [17] produced elevations of the RS-T interval in the limb leads of the electrocardiogram of dogs by applications of pitressin to the heart, as well as by the intravenous injection of this drug. The changes that they report are the typical changes in the left posterior circumflex artery. It is probable that this artery took part in the general coronary vasoconstriction which occurred in their experiments, since in our work this vessel was the only one that would produce an elevation of the RS-T interval in the limb leads.

We have not studied the electrocardiographic phenomena of infarction confined to the ventricular septum. The septal branch of the left anterior descending coronary artery, which supplies this part of the heart, lies deeply, and its operative approach is difficult. Kahn,[18] however, developed a technic for occluding this vessel. His tracings, although complicated by ischemia of the branches of the bundle of His, show a definite depression of the RS-T interval of the electrocardiogram in lead II.

17. Gruber, C. M., and Kountz, W. B.: Electrocardiogram of Non-Anesthetized Dogs as Modified by Intravenous Injection of Pitressin, Atropine Sulphate and Vagus Section, J. Pharmacol. & Exper. Therap. **40**:253 (Nov.) 1930; The Electrocardiographic Changes in Anoxemia, Proc. Soc. Exper. Biol. & Med. **27**: 170 (Dec.) 1929; Effect of Pitressin upon the Heart, ibid. **27**:161 (Dec.) 1929.

18. Kahn, R. H.: Elektrokardiogrammstudien, Arch. f. d. ges. Physiol. **140**: 627 (June) 1911.

It might be well to record here the relative immediate danger to the dog of clamping the various coronary arteries. Ventricular fibrillation is the usual terminal event in experiments on coronary occlusion. It occurs most rapidly when the left posterior circumflex artery is occluded, within three or four minutes as a rule. It develops more slowly after obstruction of the left anterior descending artery. The least danger of early fibrillation seems to result from right coronary occlusion.[19] Clamping of both the right and the left anterior descending arteries did not seem to be as immediately dangerous to the life of the animal as clamping of the left posterior circumflex alone. We do not understand the reason why occlusion of the latter artery should be particularly prone to cause ventricular fibrillation. The question arises as to whether there is an area in the distribution of this artery which, when deprived of its blood supply, is especially likely to cause fibrillation of the ventricles. The coronary sinus and the inferior vena cava may be clamped for relatively long periods without endangering the life of the animal.[5]

Our previous observations[3a] concerning extrasystoles in experimental coronary occlusion have been confirmed. This type of arrhythmia almost never appears during the first two minutes after obstruction of a coronary artery. It appears later, and is often an indicator of imminent ventricular fibrillation. It is possible that our results have differed from those of other observers either because of the type of anesthesia used, or on account of our care to avoid mechanical stimulation of the myocardium.

Other disturbances of rate and rhythm of the heart were observed. Simple bradycardia, with or without ventricular escape, was noted after occlusion of the right coronary artery and obstruction of the vena cava. Occlusion of the left posterior circumflex artery frequently produced heart block. Auricular fibrillation and paroxysms of auricular and ventricular tachycardia were seen occasionally.

SUMMARY

1. The dog presents a situation analogous to that existing in man, with respect to occlusion of the coronary arteries. Infarction in some parts of the heart produces a deviation of the RS-T interval from the iso-electric line in the conventional electrocardiogram. Infarction in other parts of the heart does not.

2. Electrograms show that the failure of certain infarcts to affect the limb lead electrocardiogram is not due to a failure of the develop-

19. The experiments of Smith[1] show a high mortality from ligation of the right coronary artery. They are, however, of a nature somewhat different from ours.

ment of changes in the action current in the infarcted area. By means of direct heart leads, deviations of the RS-T interval are recordable within a few minutes after infarction of any part of the surface of the heart.

3. If conduction from all surfaces of the heart is adequate and if an anteroposterior chest lead is used in addition to the routine limb leads, a deviation of the RS-T interval can be recorded in one or more leads after occlusion of any one of the three main coronary arterial trunks. This is likewise true of occlusion of some of the branches of these arteries.

4. Deviation of the RS-T interval due to occlusion of the left anterior descending coronary artery appears in only one of these four leads, the anteroposterior chest lead. Likewise, in man, infarcts in some parts of the heart fail to produce deviations of the RS-T interval except in certain leads which heretofore have not been used as a routine measure.

5. When the right and the left arm lead wires are used and when the electrodes are placed on opposite sides of the chest, an infarct located beneath the former produces a depression of the RS-T interval; one located beneath the latter produces an elevation of this interval. The direction of the deviation of the RS-T interval and the lead in which it makes its maximum appearance serve to indicate the location of the infarct. It is therefore probable that more accurate electrocardiographic localization of myocardial infarcts may be attained in man by the use of chest leads in addition to the three conventional ones.

6. Deviations of the RS-T interval after coronary occlusion in the dog appear within two minutes. It is not likely that they take much longer to appear in man.

7. No additional impairment of the coronary circulation or of the general circulation is necessary for the production of deviation of the RS-T interval beyond that produced by occlusion of a coronary artery.

8. The size of an infarct necessary to cause changes in the RS-T interval, recordable from the body surface, has not been determined accurately. It is certain, however, that relatively small infarcts suffice. The optimum points of application of the electrodes for recording electrocardiographic changes after obstruction of the various coronary arteries deserves further investigation.

9. This series of experiments demonstrates that in the dog deviation of the RS-T interval from the iso-electric line is a characteristic result of acute infarction of any part of the surface of the heart. Failure to record this electrocardiographic change in previous similar experiments

has often been due to failure to apply the electrodes to the surface of the body in the proper locations.

The necessity for augmenting the three conventional leads is apparent if a more nearly adequate electrocardiographic picture of cardiac events is to be obtained.

These experiments were carried on in the Surgical Research Laboratory of the Medical School of the University of Pennsylvania. Dr. I. S. Ravdin placed these facilities at our disposal:

IMMUNE REACTIONS IN DIABETES

JOHANNES K. MOEN, M.D.
AND
HOBART A. REIMANN, M.D.
MINNEAPOLIS

The unfavorable effect of intercurrent infection on diabetes has long been observed. Joslin [1] drew attention to the presence of infection in nearly every case of coma in the pre-insulin era. At present, a diminution of the effectiveness of insulin during infection is common experience.[2a] Although many studies have been devoted to the effects of infection on diabetes, less attention has been given to the underlying cause of the apparent increased susceptibility of diabetic patients to infection. As the number of deaths from coma have decreased within the past decade, the relative incidence of deaths from various infections has increased. In one series,[1] death from infection during diabetes has increased from 8.5 per cent in the Naunyn era to 26.8 per cent at present. Infection, not including tuberculosis and syphilis, was the cause of death in 126 of Warren's [2b] 300 fatal cases. He remarked that whereas arteriosclerosis threatens the diabetic patient who is doing well, infection is the chief danger of patients who are doing poorly. Among his cases, the susceptibility to infection was in proportion to the severity of the diabetes.

Various experimental studies have been made to determine the cause for the decreased resistance of diabetic persons to infection. One of the most popular theories developed in 1904 from the studies of Lassar,[3] who believed that the increased sugar content of the blood and tissues especially favored the growth of staphylococci. Handmann,[4] on the other hand, showed that blood containing 0.5 or 1 per cent of dextrose did not provide better growth conditions for staphylococci in vitro than normal blood. He also showed that the addition of sugar to the blood within limits found in diabetic patients did not decrease the bactericidal power of the serum. He believed that the diminished resistance of most

From the Department of Medicine, University Hospital, University of Minnesota.

1. Joslin, E. P.: Treatment of Diabetes Mellitus, ed. 4, Philadelphia, Lea & Febiger, 1928.

2. Warren, S.: (*a*) Pathology of Diabetes Mellitus, Philadelphia, Lea & Febiger, 1930; (*b*) p. 154; (*c*) p. 102.

3. Lassar, O.: Dermat. Ztschr. **11**:189, 1904.

4. Handmann, E.: Deutsches Arch. f. klin. Med. **102**:1, 1911.

diabetic persons to infection was a problem of cellular rather than of humoral immunity. Recent studies by Hirsch-Kauffmann and Heimann-Trosien [5] showed that hyperglycemic blood from diabetic children without acidosis did not cause an increase of bacterial growth as compared with blood from normal persons, but blood from 3 comatose patients significantly stimulated bacterial growth. The addition of dextrose and acetone bodies apparently was not alone responsible for increased growth, nor could the growth of bacteria be stimulated by hyperglycemia, lipemia or acidosis produced artificially. Rosenthal and Behrendt [6] showed that the addition of pus to insulin in vitro abolished the usual effectiveness of insulin in reducing blood sugar when injected into experimental animals.

Other investigators have approached the problem from a different angle. Observations have been made in regard to variations of complement and opsonic index in experimentally depancreatized animals and in diabetic patients. Sweet,[7] working with dogs, found a marked decrease of hemolytic and bacteriolytic complement in pancreatectomized animals. He noted that transient glycosuria produced by phlorhizin or epinephrine caused no change in complement. Rockwood and Beeler [8] found no significant variation of serum complement in diabetic patients. According to the experiments of Da Costa [9] and of Da Costa and Beardsley,[10] the average opsonic index tested with a variety of bacteria was reduced about 30 per cent below the normal in diabetic patients. Bayer and Form [11] noted that insulin increased phagocytosis in vitro. Following pancreatectomy, they [12] observed that a decrease of hemolytic complement was temporarily restored to normal by the injection of insulin and dextrose. In several complicated experiments, Nozaki [13] showed that the typhoid bacillus agglutinin titer of vaccinated rabbits is temporarily increased by the injection of insulin.

In experiments of a different nature [14] in other diseases that are characterized by the frequency of intercurrent infection, it was shown that the formation of agglutinins was markedly retarded as compared

5. Hirsch-Kauffmann, H., and Heimann-Trosien, A.: Klin. Wchnschr. **5**: 1922, 1926.

6. Rosenthal, F., and Behrendt, R.: Ztschr. f. d. ges. exper. Med. **53**:562, 1926.

7. Sweet, J. E.: J. M. Research **10**:255, 1903.

8. Rockwood, R., and Beeler, C.: Complement in Serum of Diabetic and Uremic Patients, J. Infect. Dis. **34**:625 (June) 1924.

9. Da Costa, J. C., Jr.: Am. J. M. Sc. **134**:57, 1907.

10. Da Costa, J. C., Jr., and Beardsley, E. J. G.: Am. J. M. Sc. **136**:361, 1908.

11. Bayer, G., and Form, O.: Deutsche med. Wchnschr. **52**:784, 1926.

12. Bayer, G., and Form, O.: Deutsche med. Wchnschr. **52**:1338, 1926.

13. Nozaki, M.: Keijo J. Med. **1**:248, 1930.

14. Chung, H. L., and Reimann, H. A.: Antibody Formation in Kala-Azar, Arch. Int. Med. **46**:782 (Nov.) 1930.

with their development in normal persons. In other words, clinical evidence of increased susceptibility to intercurrent infection coincided with evidence of diminished antibody response to injected antigens. It was assumed that similar studies might be of value when applied to diabetic patients.

METHODS

Twelve diabetic patients and six normal persons for control who had never had typhoid fever, who had never been vaccinated and who were apparently free from other infection were vaccinated with "triple typhoid" vaccine in the usual manner; that is, 0.5, 1 and 1 cc. of vaccine containing 1,000 million heat-killed Bacillus typhosus and 750 million each of B. paratyphosus A and B per cubic centimeter (prepared by the Division of Preventable Diseases, Minnesota Department of Health) was injected subcutaneously at five day intervals. Because of the large amount of technical work involved, it was found convenient to observe groups of

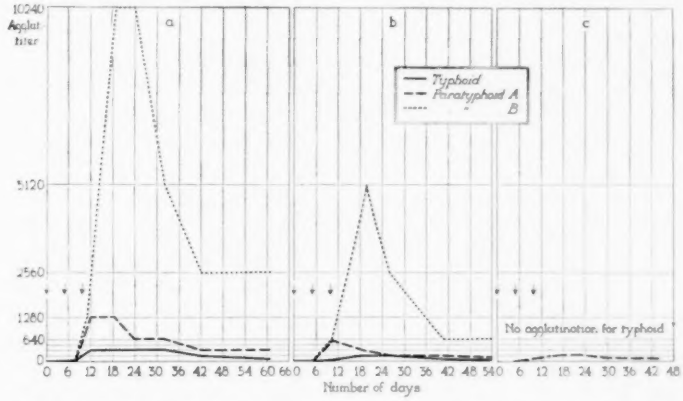


Chart 1.—The agglutinin response following vaccination with typhoid-paratyphoid A and B vaccine in a normal subject (*a*), in a controlled case of diabetes (*b*) and in a severe case of diabetes with acidosis (*c*). The arrows indicate the time of vaccination.

four diabetic patients and two control subjects in separate experiments. Blood was obtained from each subject before each injection of vaccine and at intervals of from five to ten days thereafter for a period of six weeks or more. Serum was removed from the clot and stored in a refrigerator until the completion of each set. Agglutination tests were then made in the usual manner, the macroscopic technic being used. In each experimental group the serums were tested for agglutinins for the three strains of bacilli separately; that is, the titer for B. typhosus in all samples of serums at hand was first tested. In the second and third tests, B. paratyphosus A and B were used, respectively, so that for the sake of uniformity the same suspension of organisms was tested in each sample of serum under similar conditions.

The time required for the acquisition and selection of diabetic patients suitable for this study necessitated the use of different lots of vaccine, so that a somewhat different antigenic response was produced in the different groups of subjects observed.

RESULTS

No harmful effects from the injection of vaccine were noted in any of the patients. There was nothing especially striking or correlative between the age of the patient, the duration of the diabetes and the severity of the local or constitutional reaction to the vaccine.

Agglutinin Formation in Normal Persons.—Agglutinins for B. typhosus and B. paratyphosus A appeared in each vaccinated subject in titers comparable to those in previous experiments [14] and in those reported by many other observers. The titer usually reached the maximum about three weeks after the first vaccination; it then fell off rather rapidly to a lower titer, which in most instances was maintained beyond the termination of the period of observation. In 5 of the controls, the maximum agglutination titer for B. typhosus varied from 160 to 1,280, and in one subject reached 20,480. The titer for B. paratyphosus A varied from 640 to 10,240; that for B. paratyphosus B in 2 groups of experiments, from 2,560 to 10,240. The agglutinin response for the 3 strains of bacilli in a normal subject is illustrated in chart 1*a*. The third experimental group received vaccine that failed to provoke agglutinins for B. paratyphosus B. Whether this was due to the low antigenic properties of the bacilli or to the absence of the antigen in the vaccine was not determined.

Agglutinin Formation in Diabetic Patients.—The 12 diabetic patients studied may be divided into: (*a*) 7 patients with cases controlled satisfactorily for periods ranging from several weeks to many months, (*b*) 2 patients in whom diabetes was uncontrolled, with persistent glycosuria, but without acidosis, and (*c*) 3 patients with severe diabetes who were first observed and vaccinated during diabetic acidosis.

The agglutinin response in the group of patients with controlled diabetes approached that of normal subjects, but in no instance did the agglutinin titer for any of the 3 strains exceed 5,120. An illustration of agglutinin titer curves in a typical controlled case is shown in chart 1*b*.

Two patients with uncontrolled diabetes showed distinctly subnormal responses to the 3 strains of bacilli. One of these patients persistently failed to adhere to the proper dietary regimen and in consequence had persistent glycosuria. The other patient had severe diabetes, requiring 75 units of insulin daily.

The most marked deviation from the normal occurred in 3 patients with severe diabetes and acidosis. In these cases the first dose of vaccine was given before the administration of insulin, while the patients were still suffering from acidosis. The 3 patients showed low agglutinin response to certain antigens and no response whatever to others. The administration of insulin and regulation of the diet subsequent to the first injection of vaccine apparently had but little effect on agglutinin

formation. One of the normal subjects used as a control for this group showed the highest titer observed—20,480 for B. typhosus and 10,240 for B. paratyphosus A.

In one of the patients, the titer for B. typhosus never exceeded 80, and that for B. paratyphosus A reached 640, but dropped to 160 at the end of the period of observation. In the second patient agglutinins failed to develop for either B. typhosus or B. paratyphosus B, while the maximum titer for B. paratyphosus A reached only 160, as shown in chart 1*c*. The third patient was admitted in a state of precoma with Kussmaul breathing, dehydration, drowsiness, nausea, vomiting and acetonuria. The acidosis and diabetes were promptly controlled with insulin. Unfortunately, the patient left the hospital fourteen days after the first injection of vaccine. At this time no agglutinin for B. typhosus had appeared, and the titer for B. paratyphosus A had reached 320.

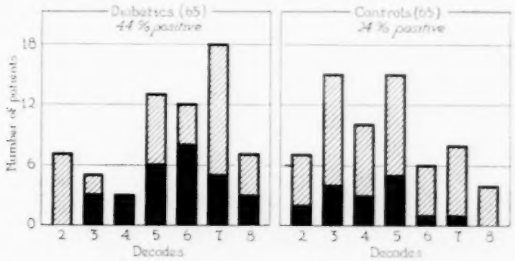


Chart 2.—The comparative reactivity of diabetic patients and control patients to the intradermal tuberculin test.

The Tuberculin Reaction in Diabetic Patients.—As a part of the study concerning immune reactions in diabetic patients, the skin reaction to tuberculin was observed in 65 diabetic patients and in 65 nondiabetic control subjects who were apparently free from evidence of tuberculosis. The control subjects were patients in a general hospital group with a variety of other diseases. The Mantoux test was used; 0.1 cc. of a 1 : 1,000 dilution of old tuberculin was injected intradermally. The skin reactions were read forty-eight hours later. Care was taken to use the same supply of tuberculin for all of the tests. A reaction was considered positive when erythema at least 1 cm. in diameter, with or without induration, appeared after forty-eight hours.

Results.—Positive reactions appeared in 29 (44 per cent) of the diabetic patients and in 16 (24 per cent) of the control patients. By dividing the subjects tested into age groups by decades, it appears that the diabetic patients who reacted positively are somewhat older than in the control groups (chart 2). The number of observations is obviously

insufficient to draw definite conclusions, but it appears at least that the percentage of diabetic patients who react positively to tuberculin is considerably higher than in the control group of nondiabetic persons.

COMMENT

The cause for the apparent diminution of agglutinin development in uncontrolled diabetic patients is obscure. Although a number of investigators have suggested that agglutinins originate in the reticuloendothelial system, in the hematopoietic system or in both,[13] it is impossible to determine definitely the exact site of origin. Experiments on the relationship of changes in the colloidal composition of the plasma to agglutination phenomena are too recent and incomplete to permit discussion in this regard.[15] Evidence exists [2c] that cells of the reticuloendothelial system in fatal cases of diabetic coma often contain abnormal substances and appear degenerated, but the changes described do not seem to warrant the assumption that these deposits materially effect the production of agglutinins. Nozaki [13] believed that the production of antibody is augmented by various hormones, including insulin. He has shown that when the agglutinin titer for typhoid bacilli in vaccinated rabbits has become constant, an injection of insulin causes a transient increase in the agglutination titer. It is possible, however, that the transient increase as reported by Nozaki may be brought about by the injection of other foreign substances.[15] We have observed the behavior of the agglutinin titer in 2 diabetic patients immediately after a subcutaneous injection of insulin. In one there was a slight increase of titer, while in the other, no change occurred.

From the results in our own series of cases it appears that the agglutinin response to injected antigens is poorest in the uncontrolled cases of diabetes, especially those approaching the state of acidosis and coma. The response is somewhat greater in controlled cases of diabetes and is best in controlled cases of diabetes in which the patients are in apparent good health. In the latter cases the response approaches, and in some cases equals, the development of agglutinins in normal persons.

It was not possible to ascribe the low agglutinin response in certain cases to any definite cause or to demonstrate specific pathologic changes that may be accountable. It is possible that a metabolic perversion or a general lowering of normal functions of the body plays an important rôle in the elaboration of antibodies. Furthermore, there appears to be a coincidence of susceptibility to infection and evidence of decreased agglutinin production in proportion to the severity of diabetes. The stronger response of patients with well controlled diabetes suggests that the deficiency of agglutinin production during the severe states of the

15. Reimann, H. A.: Ann. Int. Med. **6**:362 (Sept.) 1932.

disease, as in the case of kala-azar,[14] is transient, and with restoration of the body toward the normal state, immune reactions approach the normal.

CONCLUSION

The development of agglutinins for typhoid bacilli after the vaccination of diabetic patients and normal persons was observed. In well patients with controlled diabetes, agglutinins developed in titers similar to those in normal persons used as controls. In patient with diabetes that was controlled with more difficulty, the agglutinin response was distinctly weaker. In patients with uncontrolled diabetes with acidosis, the agglutinin response was poor; in a few cases no agglutinin for certain strains appeared. The coincidence of the increased susceptibility of severely ill diabetic patients and the deficiency of demonstrable antibodies suggests a causal relationship of the latter to the former condition.

EFFECT OF ANOXEMIA ON THE EMPTYING TIME OF THE STOMACH

EDWARD J. VAN LIERE, PH.D., M.D.
GEORGE CRISLER, PH.D., M.D.
AND
DENNIS ROBINSON, B.S.
MORGANTOWN, W. VA.

The rapid development of travel by airplane has brought to a large number of people a new physiologic environment. A few years ago only the professional balloonist and the mountain climber were subjected to high altitudes, but in recent years the number of people who are subjected to anoxemia has been steadily increasing. From this point of view alone the effect of low oxygen tension on the stomach would be of interest. This combined, however, with the fact that anoxemia is also caused by the various anemias, by diseases of the circulation and of the lungs makes the problem still more interesting. It is well known, for example, that gastric disturbances are not uncommon with cardiac disorders.

It was shown by the authors of this paper in 1930 [1] that hunger contractions in the normal dog were greatly decreased in anoxemia. In a subsequent paper [2] it was shown that under similar conditions digestive peristalses, too, were markedly diminished, and that the muscle tone of the stomach was appreciably lowered. As far as we are aware, this work is all that is found in the literature on the motility of the intact gastro-intestinal tract under anoxemic conditions. As hunger contractions and digestive peristalses were both lessened when anoxemia was induced, it was thought well worth while to ascertain the effect of lowered oxygen tension on the emptying time of the stomach.

METHOD

Six normal dogs averaging about 6 Kg. in weight were given a meal consisting of 40 Gm. of hamburger steak, 10 Gm. of dried ground bread and 50 cc. of milk; 15 Gm. of barium sulphate was added. The dogs ate this meal with relish. They were then put into a large steel respiratory chamber which could be tightly closed. It was well ventilated, however, by means of an air pump which was kept con-

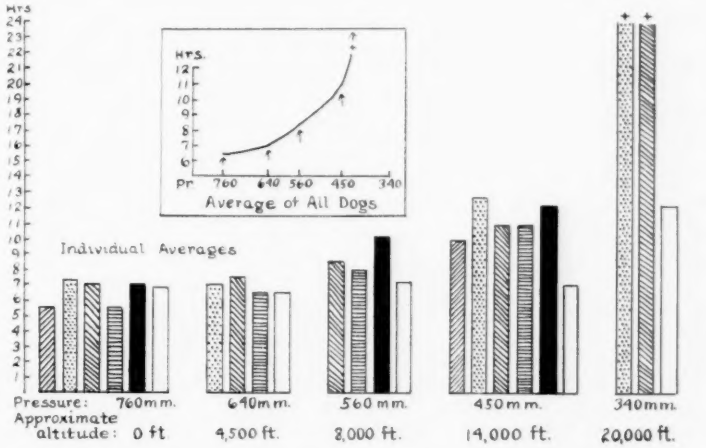
From the Department of Physiology, University of West Virginia, Morgantown.

1. Van Liere, E. J., and Crisler, G.: The Effect of Anoxemia on Hunger Contractions, Am. J. Physiol. **93**:267 (May) 1930.

2. Crisler, G., and Van Liere, E. J.: The Effect of Anoxemia on the Digestive Movements of the Stomach, Am. J. Physiol. **102**:629 (Dec.) 1932.

stantly running. The air was drawn out, but a valve opposite the opening through which the pump withdrew the air was left open so that a stream of fresh air was continually flowing through the tank. During the control periods the inside of the chamber was, of course, kept at atmospheric pressure. By means of the fluoroscope the normal emptying time of the stomach was determined for each dog; this was done for a number of days. It was obviously necessary to remove the animals from the chamber in order to examine them under the fluoroscope. This procedure took from five to fifteen minutes, so that an experimental error of thirty minutes was allowed, that is, plus or minus fifteen minutes.

After the control periods were well established, the animals were subjected to a lowered oxygen tension. This was done by partially closing the valve which opened to the outside air so that the pump could withdraw the air somewhat faster than it could enter. The valve was adjusted to whatever pressure was desired.


Hrs.
Hrs.
Pr 760 640 560 450 340
Average of All Dogs
Individual Averages
Pressure: 760mm. 640mm. 560mm. 450mm. 340mm.
Approximate altitude: 0 ft 4,500 ft. 8,000 ft. 14,000 ft. 20,000 ft.

Effect of anoxemia on the individual emptying time of the stomach in six animals at various pressures. Each animal is represented by the same type of shading under each pressure at which emptying occurs.

In order to obtain the pressure within the chamber, a long glass U-tube filled with mercury up to a level of 380 mm. was attached to a meter stick. This mercury manometer was connected with the chamber; the pressure fell as the air was exhausted, and it could be read directly in millimeters of mercury. The large capacity of the air pump provided good ventilation and prevented the accumulation of carbon dioxide, in spite of the fact that the inlet valve was partly closed.

RESULTS

The accompanying illustration shows the results obtained. The normal emptying time of the stomach varied, but was characteristic for each dog. In the case of two dogs the time was five and one half hours, while in the other four dogs it was longer—from six and three fourths to seven and one half hours. At an air pressure of 640 mm. of

mercury there was no predictable lengthening of the emptying time of the stomach; in fact, two of the four dogs which were subjected to this pressure showed a slight decrease in the emptying time. At a pressure of 450 mm. of mercury, five of six dogs showed a considerable lengthening of the emptying time, requiring as much as five additional hours. Finally, at a pressure of 340 mm. of mercury, two of the three animals which were run at this pressure on fluoroscopic examination still showed food in their stomachs at the end of twenty-four hours, and the animal which had been resistant up to this time now also showed a distinct increase in the emptying time. These results are summarized in the table.

Effect of Anoxemia on the Emptying Time of the Stomach

	Pressure in Mm. of Mercury				
Dog	760	640	560	450	340
	In Hours				
1	5.50	....	....	10.00	....
2	7.50	7.00	....	12.75	24+
3	7.00	7.50	8.50	11.00	24+
4	5.50	6.50	8.00	11.00	....
5	7.00	....	10.25	12.25	....
6	6.75	6.50	7.25	7.00	12.50
	Per Cent of Normal				
1	100	...	...	182	.....
2	100	93	...	170	320+
3	100	106	121	157	343+
4	100	118	145	200	.....
5	100	...	146	175	.....
6	100	96	107	104	185

COMMENTS

It might appear that the normal emptying time of the stomach in these dogs was rather long, as other writers have reported shorter periods. These workers, however, used a different type of meal. We felt that a meal consisting of hamburger steak and bread and milk was a fairly well balanced diet, and, moreover, the milk gave the meal a desirable consistency. In order to check our control periods, animals were kept in the chamber so that they would be in the same environment; the pressure in the chamber was, of course, atmospheric, and, as mentioned, adequate ventilation was provided.

It is interesting to note that two of four animals showed a slight decrease in the emptying time of the stomach at a pressure of 640 mm. of mercury. It would seem that a slight stimulation occurred; further work is needed on this particular point. At a pressure of 560 mm. of mercury three of four animals showed a delay in the emptying time of the stomach. This pressure corresponds approximately to 15.35 per cent of oxygen and to an altitude of 8,000 feet. This may be taken as the threshold; there are many regions in southwestern United States that approach this altitude. It would be of interest to know whether any clinical observations have been made on this point.

At a pressure which corresponds to about 14,000 feet and to an oxygen percentage of 12.50, all the animals but one were markedly affected. This is about the altitude of Pike's Peak in Colorado. It is a well known fact that many tourists are afflicted with mountain sickness and often vomit when they arrive at the summit of Pike's Peak. No retching or vomiting movements were noticed in the dogs, but of course they were not subjected to exercise, and it is quite possible that in the case of human beings psychic factors may enter.

At an altitude of 20,000 feet, two animals still showed considerable food in their stomach at the end of twenty-four hours. This is of particular interest, as human beings can get along well at an altitude of 18,000 feet; for example, the natives of Peru, who live in the high Andes; acclimation would enter here without doubt, but to prove this point further work is required.

Owing to the lack of a proper chamber, the work could not be carried out in man, but we feel that man would react in the same way. We hope at some later time to be able to check the results on man.

The cause of the retention of food in the stomach when an animal is subjected to anoxemia is not entirely clear. There are a number of things to consider, such as the circulation of the blood, the reaction of the blood, the question of so-called vagospasm, the question of physiologic oxidations and the like. At the present time, work is in progress to determine the exact mechanism.

SUMMARY AND CONCLUSIONS

It was found that under carefully controlled conditions, dogs showed a definite prolongation of the emptying time of the stomach under anoxemic conditions. At a pressure of 560 mm. of mercury, which corresponds to an oxygen percentage of 15.35 and to an altitude of 8,000 feet, three of four dogs showed a definite retention of food in the stomach; one dog was resistant. This animal, however, responded to higher degrees of anoxemia. This, then, may be considered the threshold for the average dog. The higher the degree of anoxemia, the greater the prolongation of the emptying time of the stomach. Finally, at a pressure of 340 mm. of mercury, which corresponds to an oxygen percentage of about 9.4 and to an altitude of 20,000 feet, two of three dogs which were subjected to this pressure still had food in their stomachs at the end of twenty-four hours. Higher degrees of anoxemia were not used.

Because of the importance of air travel, and because many diseases with which man is afflicted cause anoxemia, it is felt that the results of these experiments are of interest in clinical medicine. The exact mechanism as yet has not been worked out; at the present time further work is in progress.

CONSUMPTION OF BLOOD SUGAR BY MUSCLE IN THE NONDIABETIC AND IN THE DIABETIC STATE

WALLACE M. YATER, M.D.

J. MARKOWITZ, M.D.

AND

RUSSELL F. CAHOON, B.S.

WITH THE TECHNICAL ASSISTANCE OF W. H. BURROWS

WASHINGTON, D. C.

It has been established for a number of years (Macleod and Pearce [1]) that the decline in blood sugar which follows complete removal of the abdominal viscera (including the liver) is the same in previously depancreatized as in normal dogs. This observation tended to support the hypothesis that the essential nature of pancreatic diabetes is not an inability of the tissues to consume dextrose. This experiment was criticized on the grounds of its unphysiologic nature and the necessity of keeping the animals under the influence of a general anesthetic. However, it was shown by Mann and Magath [2] in their classic studies on liverless dogs that the decline of blood sugar following hepatectomy is speedier in diabetic dogs than in normal ones. Moreover, Mann and Magath reported an experiment in which complete pancreatectomy was accomplished in a dog which by previous operations had been subjected to a marked reduction in the size of its functioning liver tissue. This animal lived for ten days on a diet of milk, during which time it had neither hyperglycemia nor glycosuria. The general condition of the animal (suppuration of the abdominal wound and the characteristic scum in the conjunctiva) indicated that it was diabetic, as did also its death at the end of ten days, which was inexplicable except on the basis of diabetes. Mann and Magath cautiously refrained from interpreting these experiments as indicating that diabetic tissues possessed an apparently normal capacity to use dextrose, although such experiments taken at their face value could not be interpreted in

---

From the Georgetown University School of Medicine.

1. Macleod, J. J. R., and Pearce, R. G.: Am. J. Physiol. **32**:184, 1913.

2. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver: II. The Effect of the Removal of the Liver on the Blood Sugar Level, Arch. Int. Med. **30**:73 (July) 1922; III. The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, ibid. **30**:171 (Aug.) 1922: IV. The Effect of Total Removal of the Liver After Pancreatectomy on the Blood Sugar Level, ibid. **31**:797 (June) 1923.

any other way. Investigators have been loath to accept such a conclusion, since strong evidence exists, on the basis of entirely different experiments, which would lead to the opposite conclusion, viz., that the essential nature of diabetes is an inability of the tissues to derive energy from the disruption of the dextrose molecule. This evidence has been summarized by Lépine according to Geelmuyden [3] as follows: (1) The administration of dextrose to depancreatized dogs is followed by its prompt quantitative elimination in the urine; (2) administration of carbohydrate to a diabetic dog does not evoke a rise in the respiratory quotient, and (3) the glycosuria of depancreatized dogs is in no way diminished by muscular exercise. We may add that the last fact is true in human beings who have severe diabetes, a condition which approximates complete pancreatectomy, although in the milder form of diabetes muscular exercise may produce an apparently greater tolerance for carbohydrate, owing to an increase in the dextrose equivalent of insulin, which F. N. Allan [4] has shown to be possible.[5]

According to the Hill-Meyerhof theory concerning the rôle of glycogen and lactic acid in muscular contraction, it is difficult to appreciate how the diabetic state could be due to inability of muscle to consume carbohydrate, since depancreatized dogs manifest a certain amount of muscular activity. However, recent work in the field of muscular contraction makes such reasoning unnecessary.

It may be taken for granted that the aforementioned experiments are entirely correct, since they have been repeated by many competent workers. Knowlton and Starling [6] investigated the consumption of dextrose by the normal and the diabetic heart, making use of the just previously developed heart-lung preparation. Their experiments were beautifully executed. They found that the heart muscle of the normal dog consumes about 4 mg. of dextrose per gram of heart muscle per hour. They stated that the power of consuming dextrose was reduced to a minimum or disappeared completely in heart-lung preparations made from animals which had been completely depancreatized several days prior to the experiment. These elegant and classic experiments were substantiated by Maclean and Smedley,[7] who perfused hearts of cats and dogs with Locke's solution and reported that when these were excised from previously depancreatized animals, little or no combustion of dextrose occurred. In spite of these findings by such reputable

3. Geelmuyden, H. C.: Ergebn. d. Physiol. **22**:92, 1923.

4. Allan, F. N.: Am. J. Physiol. **67**:275, 1924.

5. In some unpublished experiments we have been able to show that severe strychnine spasms in depancreatized dogs augment, if anything, the glycosuria.

6. Knowlton, E. P., and Starling, E. H.: J. Physiol. **45**:146, 1912.

7. Maclean, H., and Smedley, I.: J. Physiol. **45**:470, 1913.

workers, their thesis slowly lost ground on the basis that the sugar estimations were unreliable and that the results were explicable on the basis of a higher glycogen content possessed by diabetic heart muscle. Quite recently Cruickshank [8] has repeated the original experiments of Knowlton and Starling under more carefully controlled conditions, completely vindicating their findings.

One is thus confronted by two sets of apparently contradictory facts: First, the liverless dog possesses the ability of using large quantities of dextrose, so that under certain artificial conditions the diabetic state may be accompanied by neither hyperglycemia nor glycosuria; second, the contracting muscle of the diabetic organism, either intact or in the form of the isolated perfused heart, has largely lost its power to obtain the energy from dextrose. Any one who has worked in this field soon becomes convinced of the essential correctness of these observations. There must be some unifying fact relieving the apparent discrepancy. This we have attempted to find in the following series of experiments.

That there is a fundamental difference in the storage capacity of the diabetic organism for dextrose is not disputed; it is indicated by the following well established observations: (1) The liver of depancreatized animals is practically devoid of glycogen (Minkowski [9]); cardiac muscle has an increased quantity of glycogen in the diabetic state (Cruickshank [10]); (2) whereas the administration of dextrose to a liverless dog is followed by a huge increase in the respiratory quotient (Markowitz,[11] Mann and Boothby [12]), the similar administration of dextrose to a depancreatized and subsequently dehepatized dog is without effect on the respiratory quotient (Markowitz [11]), although in such animals hypoglycemic symptoms develop to which dextrose is an antidote. Soskin [13] recently reported experiments in which completely depancreatized dogs were carefully nursed and fed, with the result that in a number of them the glycosuria largely disappeared. Such animals, it is certain, were completely depancreatized.

From this brief review it is apparent that we are by no means clear as to why under certain conditions diabetic tissues appear to use dextrose and under others appear to have lost this power. We wish to present the thesis, which has inevitably unfolded itself during our experiments, that resting diabetic muscle possesses a power to consume dextrose which is practically, if not completely, indistinguishable from

8. Cruikshank, E. W. H.: Am. J. Physiol. **90**:322, 1929.
9. Minkowski, O.: Arch. f. exper. Path. u. Pharmakol. **21**:1, 1886.
10. Cruickshank, E. W. H.: J. Physiol. **47**:1, 1913.
11. Markowitz, J.: Am. J. Physiol. **83**:698, 1928.
12. Mann, F. C., and Boothby, W. M.: Am. J. Physiol. **87**:486, 1928.
13. Soskin, S.: J. Nutrition **3**:99, 1930.

that of normal muscle. When muscular contraction occurs, however, the extra metabolism imposed on the muscle does not occur by the utilization of blood sugar. It would appear that before dextrose is available to supply energy for muscular contraction it must undergo some sort of elaboration, brought about by insulin. This thesis harmonizes two apparently conflicting sets of experiments. It does not confute the great probability that in the diabetic state dextrose cannot be stored as glycogen in the absence of insulin, a fact that has been well established by Best, Dale, Hoet and Marks.[14]

I. COMPARISON OF THE CONSUMPTION OF DEXTROSE BY THE NON-DIABETIC AND THE DIABETIC HEART-LUNG PREPARATION

We have repeated the experiments of Knowlton and Starling, and find on comparing our data with theirs that the results are identical. The following protocols are typical examples.

1. *Consumption of Dextrose by the Heart-Lung Preparation (Working Muscle).*—On June 17, 1931, a heart-lung preparation was made from a dog weighing 10.2 Kg. The heart-lung apparatus contained 150 cc. of heparin in Ringer's solution, most of which was introduced into the animal via the superior vena cava to render its blood incoagulable prior to opening the artificial circuit. It was carefully calculated that 500 cc. of slightly diluted blood was obtained from the animal at the moment of complete isolation of the circuit. The blood in the pulmonary circulation and in the chambers of the heart was included in this estimate. The volume output was adjusted to 1,000 cc. per minute. This quantity was obtained by tying the aorta distal to the cannulated brachiocephalic artery and elevating the posterior extremity of the dog until practically no more blood flowed into the venous reservoir. The inferior vena cava was then tied. A mark was made to indicate the level of blood in the venous reservoir for future calibration, and blood was admitted to the superior vena cava from the reservoir, thus establishing the artificial circuit. The root of one lung was occluded by gastro-enterostomy (Doyen) forceps to minimize loss of blood in the form of pulmonary edema. The temperature of the blood in the venous reservoir was kept constant at 37 ± 0.5 C. The peripheral resistance aggregated 90 mm. of mercury, as measured by a mercury manometer connected to the cannula in the brachiocephalic artery. At 11:50 a.m., immediately after isolating the circuit, the blood sugar[15] was 0.272 per cent. This hyperglycemia is constant in all such experiments owing to asphyxial glycogenolysis in the liver. A sample of blood was collected in a test

14. Best, C. H.; Dale, H. H.; Hoet, J. P., and Marks, H. P.: Proc. Roy. Soc., London, s.B, **100**:32, 1926.

15. The Shaffer-Hartmann method (Shaffer, P. A., and Hartmann, A. F.: J. Biol. Chem. **45**:365, 1921) for the estimation of blood sugar was used in all experiments. Blood proteins were precipitated according to the Folin-Wu method, and the copper reduction values were transformed to dextrose by means of the table of W. F. Duggan and E. L. Scott (J. Biol. Chem. **45**:365, 1926), a necessary condition for the accurate use of the Shaffer-Hartmann method, since the tables of Shaffer and Hartmann are somewhat inaccurate when tested with pure solutions of dextrose.

tube which was stoppered and incubated in the blood of the venous reservoir as the control sample for glycolysis. At 12:20 p. m. the blood sugar was 0.240 per cent; at 12:50 p. m., 0.190 per cent; at 1:30 p. m., 0.158 per cent, and at 1:50 p. m., 0.110 per cent. The experiment was now terminated and the sample of blood incubated for glycolysis was then estimated for sugar content, which was 0.248 per cent. The disappearance of sugar by glycolysis was, therefore, 0.024 per cent. This figure was added to the final blood sugar estimate obtained, which made it 0.134 per cent. Therefore, 0.138 per cent blood sugar had disappeared (first blood sugar value minus 0.134) owing to contraction of the heart muscle (neglecting the metabolism of the lungs). At the end of the experiment the heart was in good condition. There was very little pulmonary edema and the experiment could have continued at least another hour. The heart was severed from the great vessels, trimmed of parietal pericardium, opened and mopped free of blood with filter paper. It weighed 88 Gm. The consumption of dextrose was therefore 3.91 mg. per gram per hour. This figure is practically identical with that obtained in other experiments performed by us and in those of Knowlton and Starling.

2. *Consumption of Dextrose by the Diabetic Heart-Lung Preparation.*—A medium-sized dog, which had been completely depancreatized four days before, was used (March 6, 1931) for a heart-lung perfusion. At 10:30 a. m. the perfusion was begun under conditions identical to those of the former experiment. The animal's own blood was used and allowed to drip into the venous reservoir up to a previously established mark, which indicated a volume in the circuit of 500 cc. When this level was attained the inferior vena cava was tied and blood was administered to the superior vena cava from the reservoir, thus completing the circuit. At 10:30 a. m. a sample of blood was taken for a dextrose estimation. The blood sugar value was 0.275 per cent. At the time that this sample was taken, some blood was collected as a control sample for glycolysis. At 11:00 a. m. the blood sugar value was 0.267 per cent. At 11:30 a. m. it was 0.233 per cent. The control sample for glycolysis at this time had a sugar content of 0.250 per cent. In the course of an hour, therefore, the blood sugar had fallen from 0.275 to 0.233 per cent, or 0.042 per cent, of which 0.025 per cent was due to glycolysis. The consumption of dextrose, therefore, was 0.017 per cent. The experiment was terminated at this point, with the preparation in good condition, and the heart was treated and weighed as in the previous experiment. The weight was 92.5 Gm. The dextrose which was consumed was estimated on the basis of a total volume of 500 cc. of blood. This equals 85 mg. of dextrose, or a consumption of 0.92 mg. per gram of heart muscle per hour, which is approximately one-fourth the normal amount. The glycogen content of the heart was determined at the end of the experiment. This was 0.720 per cent.

The experiments so adequately confirm those of Knowlton and Starling that it may be taken as established that, whereas normal heart muscle consumes 4 mg. dextrose per gram per working hour under the conditions described in a heart-lung circuit, the heart muscle of a previously depancreatized dog under identical conditions consumes under one-fourth this quantity. It may be argued that the meager consumption of blood sugar by the diabetic heart is an accident, depending on the greater quantity of glycogen contained by the heart in diabetes. This explanation, plausible though it is, must be rejected for

the following reasons, based on the observations of Knowlton and Starling [6] and Cruickshank.[8] When the diabetic heart is perfused with normal blood (i. e., removed from a nondiabetic donor) its sugar consumption is normal. The same occurs when insulin is added to the blood of the diabetic heart-lung preparation. It will be shown later that the rate of consumption of blood sugar by diabetic heart muscle corresponds to the rate of consumption of blood sugar by the resting muscle of a liverless dog. A liverless dog requires 250 mg. per kilogram per hour for the blood sugar to stay normal. Assuming that the seat of oxidation of blood sugar (Mann and Magath) in a liverless animal is chiefly muscle, which is approximately one third of the body weight, it can be calculated that the consumption of blood sugar by resting skeletal muscle is 250 divided by 3, which equals 0.83 mg. per gram per hour. This calculation is, of course, only approximate, since it does not take into account the dextrose consumption of the brain and of other tissues, which, however, are not nearly as bulky. Nevertheless, the general deduction seems inescapable that contracting diabetic muscle (heart) consumes about as much sugar as does resting nondiabetic skeletal muscle per unit weight. Blood sugar apparently is not available in the diabetic state for the purpose of yielding energy for muscular contraction of the heart. Probably one function of insulin is to elaborate the dextrose molecule so that it can serve this purpose.

To obtain further information regarding the plausibility of this hypothesis we undertook to estimate the dextrose requirements of liverless dogs both in the nondiabetic and in the diabetic state and during the conditions of rest and vigorous muscular activity. For this purpose we made use of the recently developed method of one-stage hepatectomy described in a forthcoming paper (Markowitz, Yater and Burrows [16]), by which it is possible to remove the liver of a dog in one stage with reasonable expectations that a vigorous long-lived preparation will result. Accordingly we excised the liver of several dogs after a preliminary fast of twenty-four hours. The subsequent behavior of these animals was identical with those of Mann,[17] prepared by the three-stage method. The decline of blood sugar following hepatectomy was studied in a series of such animals. In another series the animals were strychninized sufficiently to induce severe convulsions for an hour or more. To accomplish this it was necessary to inject 0.20 mg. of strychnine sulphate per kilogram of body weight intravenously and one quarter of this dose subcutaneously at intervals of fifteen minutes or so, to maintain the animal in the convulsive state.

16. Markowitz, J.: Yater, W. M., and Burrows, W. H.: A Simple One-Stage Technic for Hepatectomy in the Dog, J. Lab. & Clin. Med., to be published.

17. Mann, F. C.: Am. J. M. Sc. **161**:37, 1921.

A number of animals were lost. No matter how severe the convulsions were, the decline of blood sugar was not accelerated. This conclusion was such a difficult one to accept that we repeated the experiments, comparing the decline in blood sugar of etherized liverless dogs with that of liverless dogs which were also kept under ether anesthesia but in which the spinal cord was stimulated thirty times each minute by faradic shocks with the resultant convulsions of the muscles, mainly of the hind limbs. This was achieved by a Lewis rotary interrupter, the stimulating electrode being inserted into the cord at the level of the sixth thoracic segment. Under these conditions also the decline in blood sugar was generally uninfluenced by the muscular contractions. Apparently the decline in the blood sugar of a liverless dog is not a satisfactory criterion of the sugar requirements of working muscle. It may well be that the carbohydrate requirements of muscle are partitioned between the glycogen of the muscle on the one hand and the blood sugar on the other, the latter being spared in hypoglycemia. The plan of experimentation was accordingly changed to the following: The liver was removed from a series of dogs and dextrose was injected intravenously either continuously or every fifteen minutes with the object of establishing the quantity necessary to maintain the blood sugar constant during the first ten hours following removal of the liver. As illustrated by the following protocol this figure is 0.25 Gm. of dextrose per kilogram per hour.

II. EFFECT ON BLOOD SUGAR OF A LIVERLESS DOG OF CONTINUOUS INTRAVENOUS INJECTION OF 0.25 GM. OF DEXTROSE PER KILOGRAM PER HOUR

A female collie, weighing 8.7 Kg., was etherized at 10:00 a. m. on Jan. 6, 1932. At 10:10 a. m. blood was removed for a dextrose estimation. This was 0.183 per cent. At 10:15 a. m. the first incision was made. At 10:40 a. m. the Eck fistula was completed, the stoma being 1.5 cm. long. At 10:48 a. m. the liver was extirpated. During the operation only 15 cc. of blood was lost, an irreducible minimum for this type of surgery. The etherization was discontinued. At 11:00 a. m. the last suture was tied. At 11:04 a. m. the blood sugar was 0.115 per cent (chart 1). By 11:20 a. m. the dog was fully conscious, and continuous intravenous injection of dextrose solution by means of a cannula in a saphenous vein was begun. The dextrose was made up in 12.5 per cent solution in physiologic solution of sodium chloride. It was injected at a constant rate by a continuous infusion apparatus, 17.4 cc. being injected every hour. By noon the animal had made a perfect recovery, the mucous membranes of the mouth being a rosy pink (a good criterion of the viability of a liverless dog). At 12:13 p. m. the blood sugar was 0.134 per cent; at 1:25 p. m., 0.100 per cent; at 3:20 p. m., 0.116 per cent, and at 5:26 p. m., 0.113 per cent (the condition of the animal was still excellent). At 8:20 p. m. the dog urinated copiously and appeared normal in every respect. At 9:00 p. m. the blood sugar was 0.116 per cent. At 10:30 p. m. the animal vomited about 30 cc. of material. At 11:50

p. m. the blood sugar was 0.089 per cent. The animal died at 3:45 a. m., on January 7, with typical "second-stage" symptoms. Necropsy revealed nothing of significance to the experiment.

This and similar experiments revealed that the blood sugar level was practically constant after uncomplicated hepatectomy for the first ten hours if the animal received 0.25 Gm. of dextrose per hour either continuously or every fifteen minutes, or indeed every hour. In the latter circumstances the blood samples were removed for analysis just prior to the injections. With this information we investigated the blood sugar content of such dehepatized dogs subjected to vigorous muscular contraction, such as, for instance, those induced by an injection of strychnine. A typical protocol follows, which is one of several similar experiments with identical results.

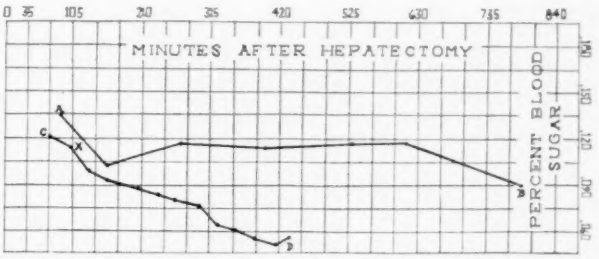


Chart 1.—Curve *AB* indicates the typical level of the blood sugar in a liverless dog receiving a continuous injection of dextrose at the rate of 0.25 Gm. per kilogram per hour. Curve *CD* indicates the typical level of the blood sugar under the same conditions except that the animal was strychninized at *X*.

III. EFFECT ON BLOOD SUGAR OF STRYCHNINIZED LIVERLESS DOG OF INJECTIONS OF DEXTROSE SOLUTION EVERY FIFTEEN MINUTES AT THE RATE OF 0.25 GM. PER KILOGRAM PER HOUR

On Jan. 18, 1932, a female dog weighing 11 Kg. was dehepatized. The operation was well done. The Eck fistula was completed at 11:10 a. m. The liver was removed at 11:20 a. m. and the last stitch placed in the skin at 11:30 a. m. The animal made a sthenic recovery, which was practically complete at 11:45 a. m. At that time the animal was given the first injection of 5.5 cc. of 12.5 per cent dextrose in saline solution by means of a cannula in a saphenous vein. Injections were given every fifteen minutes. The blood sugar sample was removed from time to time just prior to an injection. At 12:30 p. m. the blood sugar was 0.120 per cent (chart 1). At 1:00 p. m., 1 mg. of strychnine sulphate was given intravenously. At 1:03 p. m., 0.5 mg. was injected. The animal was only mildly hyperexcitable and at 1:06 p. m. was given an additional 0.25 mg. of the drug. At 1:03 p. m. the blood sugar was 0.113 per cent. At 1:07 p. m. violent generalized tetanic convulsions developed which persisted until 1:15 p. m.

During this time the spasms were sufficiently severe to necessitate artificial respiration. By 1:20 p. m. the convulsion had subsided completely, but by 1:45 p. m. the animal was still breathless from the exertion. At 2:00 p. m. it was still hyperexcitable to tactile stimulation. Meanwhille the blood sugar values were as follows: at 1:30 p. m., 0.097 per cent; at 2:00 p. m., 0.092 per cent; at 2:45 p. m., 0.087 per cent; at 3:15 p. m., 0.084 per cent; at 3:45 p. m., 0.080 per cent; at 4:15 p. m., 0.077 per cent; at 4:45 p. m., 0.063 per cent; at 5:14 p. m., 0.060 per cent; at 5:44 p. m., 0.056 per cent; at 6:14 p. m., 0.053 per cent, and at 6:44 p. m., 0.056 per cent. This animal was still hyperexcitable by 5:13 p. m. (This prolonged hyperexcitability vindicates the contention of Priestley, Mann and one of us [Dr. Markowitz][18] that the liver plays a major rôle in the destruction of strychnine and that the liverless animal is more susceptible to strychnine.) The animal voided large quantities of urine several times during the experiment. At 6:50 p. m. it was in fair condition and was killed. The observations at necropsy were essentially negative.

In consequence of the Hill-Meyerhoff theory concerning the essential rôle of carbohydrate in the development of muscular tension, it has largely come to be assumed that contracting muscle derives at least a part of its energy from blood sugar. This contention received support from the classic experiments of Locke and Rosenheim,[19] who showed that perfused (nonworking) cardiac muscle consumed dextrose at a rate of approximately 1.0 mg. of dextrose per gram per hour. This was the first indication that living tissue could make use of the simple dextrose molecule to supply its energy requirements. This fact is of historical importance. Minkowski[9] in his work on liverless geese, and Mann and Magath with liverless dogs, showed that the well-being and indeed the life of the organism were affected when the sugar content of the blood was diminished. The experiment just recorded by us is an addition to this information, proving that contracting skeletal muscle withdraws much greater quantities of sugar from the blood than does resting muscle.

It became necessary at this stage of our experiments to determine what were the sugar requirements of depancreatized dogs which were dehepatized in the fully diabetic state. When the liver is extirpated from diabetic animals forty-eight or more hours after pancreatectomy, the blood sugar, as Kausch,[20] Macleod and Pearce and Mann and Magath have shown, shows the usual decline, from which the conclusion is inevitable that diabetic tissues in the resting condition have the normal power of consuming dextrose. Lusk and his pupils have consistently ignored the possibility that the diabetic organism can oxidize

18. Priestley, J. T.: Markowitz, J., and Mann, F. C.: Am. J. Physiol. **96**: 696, 1931.

19. Locke, F. S., and Rosenheim, O.: J. Physiol. **36**:205, 1907.

20. Kausch, W.: Arch. f. exper. Path. u. Pharmakol. **39**:219, 1897.

dextrose. Their stand has been based almost entirely on two facts: (1) The respiratory quotient of fully diabetic dogs is 0.71 (the theoretical respiratory quotient of fat oxidation); (2) ingested dextrose is quantitatively excreted in the urine. It has been pointed out by several workers that this stand is not worthy of credence. What is called the respiratory quotient is merely a hypothesis. Although none is more appreciative than we are of Lusk's contributions to science, we feel that he is here in error. Diabetic tissue has been shown by a number of workers, including us, to be capable of utilizing considerable quantities of dextrose and we feel that arguments based on such uncertain grounds as the respiratory quotient are not applicable in refuting this fact. It may be argued that part of the decline in blood sugar is due to the urinary excretion of sugar. The following protocol illustrates that diabetic tissue consumes large quantities of dextrose even when there is no possibility of the excretion of dextrose in the urine.

IV. THE DECLINE OF BLOOD SUGAR FOLLOWING THE REMOVAL OF ALL OF THE ABDOMINAL VISCERA IN THE COMPLETELY DIABETIC DOG

On June 3, 1931, a dog weighing 8 Kg. was completely depancreatized. On June 6 it was in fair condition and weighed 7 Kg. The animal was etherized on this date and the abdominal viscera were completely removed except for the suprarenal glands and the urinary bladder. The operation was accomplished as follows: The two kidneys were first removed. The celiac axis and superior mesenteric artery were tied as they originated from the aorta at the left crus of the diaphragm. The inferior mesenteric artery was then tied, being found traversing the middle of the descending mesocolon. The rectum was clamped and cut, the anal stump being tied with stout packing cord. The root of the mesentery was next cut until the superior mesenteric artery and celiac axis were reached, these being again ligated and cut distal to the ligature. The structures in the lesser omentum were cut between clamps. The lower esophagus was transected between clamps and tied. The alimentary canal was then removed from the abdomen. The liver was removed by tying and cutting the inferior vena cava below and above the liver. The abdomen was packed with moist Turkish towels and the abdominal wall closed with three layers of sutures. Animals usually make a good recovery after such procedures, and walk about after the anesthesia is over. At 9:35 a. m., when the animal was first etherized, the blood sugar was 0.336 per cent. At 10:17 a. m., when the last stitch was placed, the blood sugar was 0.316 per cent. By 10:33 a. m. the animal had completely recovered. At 10:45 a. m. the blood sugar was 0.259 per cent (chart 2). At 11:30 a. m. it was 0.205 per cent; at 12:30 p. m., 0.130 per cent; at 1:30 p. m., 0.063 per cent, and at 2:15 p. m., 0.046 per cent (the animal was barely conscious). At 2:16 p. m. the animal was given 0.5 Gm. of dextrose per kilogram in 25 per cent solution. It improved and was able to stand. At 2:30 p. m. it was killed. Observations at necrospy were essentially negative.

This experiment and similar ones demonstrate that diabetic tissue uses dextrose. At first sight it would appear that the extent of utilization might be normal. To obtain information on this point the effect on the level of the blood sugar was determined when 0.25 Gm. of dextrose in solution per hour was injected into liverless dogs which previously had been completely depancreatized.

A few words are necessary concerning the general condition of dogs that are dehepatized in the fully diabetic state. Such animals recover from the hepatectomy well, but in most instances their condition soon becomes poor. At this stage they often have a clinical picture resembling hypoglycemia, but when the blood sugar is estimated this is found

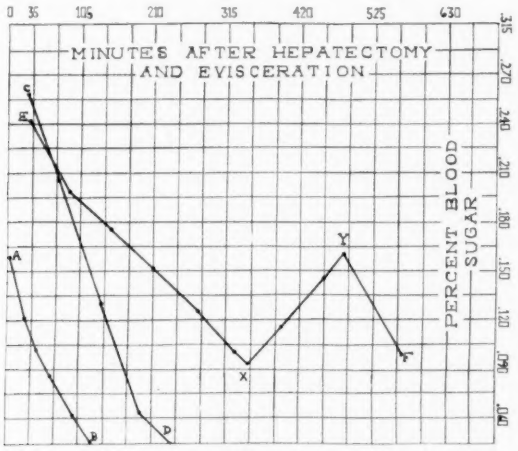


Chart 2.—Curve *AB* shows a decline in the blood sugar of a totally eviscerated dog (not mentioned in the text); this is inserted for comparison with curve *CD*. Curve *CD* shows a decline in the blood sugar of a totally eviscerated dog depancreatized four days previously. Note the precipitate decline in blood sugar, in spite of the absence of the kidneys. Curve *EF* shows the decline in blood sugar following hepatectomy in a dog depancreatized three days previously. At *X* the injection of dextrose at the rate of 0.25 Gm. per kilogram per hour was started. At *Y* the injection was discontinued. The rapid decline in blood sugar is promptly resumed.

to be over 0.1 per cent. The injection of dextrose effects a transitory recovery, and it is uncertain whether this is due to the dextrose or to the increase of blood volume. In a few cases, however, fully diabetic subjects withstand hepatectomy sufficiently well to be in good condition and fully conscious until typical hypoglycemic blood sugar values are attained. These are the most suitable for studying the extent to which diabetic tissue consumes dextrose. Mann and Magath have drawn

attention to the fact that liverless diabetic dogs usually succumb long before the blood sugar has attained a true hypoglycemic level, there being a transitory restoration to an apparently normal condition following the injection of dextrose. There can be no question, however, that an occasional subject is more viable and lasts to the hypoglycemic level.

We have no explanation to offer for the limited survival period which is the rule following extirpation of the liver in the fully diabetic state. One experiment is reported that was technically flawless and in which the animal survived for ten hours after hepatectomy.

V. EFFECT ON BLOOD SUGAR OF INJECTING DEXTROSE AT THE RATE OF 0.25 GM. PER KILOGRAM PER HOUR IN A PREVIOUSLY DEPANCREATIZED LIVERLESS DOG

On Jan. 22, 1932, a dog weighing 15.5 Kg. was completely depancreatized. On January 25 it weighed 14 Kg. and was dehepatized under ether anesthesia. At operation the liver appeared very fatty, as is usual in diabetes of this duration. The Eck fistula was completed at 10:50 a. m. and the extirpation at 11:00 a. m. A noisy, sthenic recovery soon followed, the animal being normal in appearance by noon. At 11:30 a. m. the blood sugar was 0.242 per cent (chart 2); at noon, 0.219 per cent; at 12:30 p. m., 0.200 per cent; at 1:30 p. m., 0.176 per cent; at 2:30 p. m., 0.152 per cent; at 3:30 p. m., 0.128 per cent, and at 4:30 p. m., 0.100 per cent. At 4:45 p. m., when the blood sugar was presumably 0.094 per cent, administration of dextrose was begun intravenously at the rate of 0.06 Gm. per kilogram every fifteen minutes. At 5:29 p. m. the blood sugar was 0.116 per cent; at 6:29 p. m., 0.144 per cent. Injections of dextrose were given until 7:00 p. m. and then discontinued. The blood sugar at this stage may be assumed to have been 0.160 per cent. In all, the animal had received 70 cc. of 12.5 per cent dextrose between 4:45 and 7:00 p. m. inclusive. At 7:10 p. m. it was in excellent condition. At 8:00 p. m. it was semiconscious and showed some of the symptoms of "second-stage" hepatic insufficiency. At 8:25 p. m. the blood sugar was 0.097 per cent, and the animal was unconscious. It was now given 0.25 Gm. of dextrose per kilogram intravenously. There was practically no improvement. At 9:00 p. m. the animal, showing typical "second-stage" symptoms, was killed. Necropsy yielded essentially negative results. During the experiment the dog was anuric.

As judged by the initial rate of decline in blood sugar the dextrose consumption of this animal was fully as great as that of the normal dehepatized dog. When the blood sugar had attained a normal value, dextrose was injected at the rate of 0.25 Gm. per kilogram per hour over a period of two hours and fifteen minutes, during which time the blood sugar increased from 100 to 160 per cent. On discontinuing the injection it fell, however, in one hour and fifteen minutes to 0.097 per cent. As judged by the effect of the injection, it would appear that the dextrose requirement of a diabetic liverless organism is slightly less than in the nondiabetic state. To keep the blood sugar normal would require 0.19 Gm. per kilogram per hour, in our opinion. The difference we believe is due to the fact that nondiabetic liverless dogs are per-

forming a certain amount of muscular exertion which consumes extra dextrose, which is also achieved by the contraction of the heart. This experiment is submitted as evidence, therefore, that the dextrose requirements of resting skeletal muscle are essentially the same in both the diabetic and the nondiabetic states.

The *experimentum crucis* for this hypothesis would be obtained by observing the dextrose tolerance of a diabetic liverless dog subjected to strychnine spasms. This we have not accomplished.

COMMENT

On the basis of experiments performed by us on liverless dogs and on heart-lung preparations in both the nondiabetic and the diabetic state, evidence is presented that the dextrose consumption of resting muscle is the same in both the diabetic and the nondiabetic state. During muscular exercise it was demonstrated that the dextrose requirement of normal muscle was increased, whereas in the diabetic state the muscular contraction did not involve an extra consumption of blood sugar. The diabetic state apparently involves a condition in which the dextrose molecule is not available for the machinery responsible for the development of tension in muscle. It would seem that the consumption of carbohydrate by muscle is of two types: (1) In the resting condition the basal requirement of dextrose is the same in both the diabetic and the nondiabetic state, and (2) in the working condition the extra consumption of dextrose is possible only in the nondiabetic state. In other words, the consumption of dextrose by working diabetic muscle is the same as that of resting diabetic muscle.

SUMMARY

1. Heart muscle in a normal heart-lung perfusion consumes 4 mg. of dextrose per gram per hour, as was previously shown by Knowlton and Starling.

2. Heart muscle in a diabetic heart-lung perfusion consumes less than one-fourth this quantity. This figure corresponds to the requirement of resting skeletal muscle of liverless dogs.

3. The decline in blood sugar following removal of the liver in dogs is the same in both the nondiabetic and the diabetic state.

4. The injection of 0.25 Gm. of dextrose intravenously per kilogram per hour in liverless dogs suffices to maintain a normal level of blood sugar, as was previously shown by Mann and Magath.

5. When liverless dogs are subjected to severe strychnine spasms the continuous injection of dextrose at this rate is insufficient to maintain the blood sugar, and it falls progressively to a hypoglycemic level in five hours.

6. When diabetic liverless dogs are given intravenous injections of dextrose at the rate of 0.25 Gm. per kilogram per hour after the blood sugar has declined to a nondiabetic level there is a slowly progressive rise of the blood sugar level. It is estimated that the blood sugar would be maintained at an approximately normal level by the injection of 0.19 Gm. of dextrose per kilogram per hour.

7. On the basis of these experiments and those quoted from the literature the hypothesis is propounded that in the diabetic state the dextrose requirement of resting skeletal muscle is the same as in the nondiabetic state, but that in the diabetic state contracting muscle is unable to utilize the dextrose molecule for the purpose of obtaining the extra energy. Apparently it is a function of insulin to elaborate the dextrose molecule so that it is available for this purpose.

News and Notes

AMERICAN MEDICAL ASSOCIATION

The Eighty-Fourth Annual Session of the American Medical Association will be held in Milwaukee, June 12 to 16. The Registration Bureau and the Scientific and Technical Exhibits will be housed in the Milwaukee Auditorium, and the Opening General Meeting will be held at the Auditorium on Tuesday, June 13, at 8:00 p. m. The readers of the ARCHIVES no doubt will be particularly interested in the following sections, which will hold sessions in the Milwaukee Auditorium on Wednesday, Thursday and Friday: Practice of Medicine (mornings), Plankinton Hall; Pathology and Physiology (mornings), North Section of Market Hall, and Pharmacology and Therapeutics (afternoons), North Section of Market Hall.

AMERICAN COLLEGE OF PHYSICIANS

The American College of Physicians will hold its eighteenth annual clinical session in Chicago, with headquarters at the Palmer House, April 16 to 20, 1934. Announcement of these dates is made not only with a view of apprising physicians generally of the meeting, but also to prevent conflicting dates with other societies that are now arranging their 1934 meetings. Dr. George Morris Piersol, of Philadelphia, is president of the American College of Physicians, and will arrange the program of general sessions. Dr. James B. Herrick, emeritus professor of medicine of Rush Medical College, Chicago, has been appointed general chairman of local arrangements and will be in charge of the program of clinics. Mr. E. R. Loveland, the executive secretary, 133-135 South Thirty-Sixth Street, Philadelphia, is in charge of general and business arrangements, and may be addressed concerning any feature of the forthcoming session.

AMERICAN HEART ASSOCIATION

The scientific session of the American Heart Association will be held on June 13, 1933, from 9:30 to 5:30 p. m. in the Knickerbocker Hotel, Milwaukee.

FIRST FRENCH CONGRESS OF THERAPEUTICS

A congress of therapeutics will take place in Paris, October 23 to 25, 1933, under the presidency of Professor Loeper, president of the Society of Therapeutics. Papers will be presented on the following subjects: (1) parenteral treatment of gastric ulcer, (2) medicinal combinations, (3) treatment of colibacillosis, (4) the epinephrines, (5) short waves in therapeutics and (6) treatment of radiodermatitis. The detailed program will be published later; for information apply to M. le Dr. G. Doin, éditeur, trésorier du Congrès, 8, place de l'Odéon, Paris, 6e.

Book Reviews

Sex and Internal Secretions. Edited by Edgar Allen. With a Foreword by Robert M. Yerkes. Price, $10. Pp. 951. Baltimore: Williams & Wilkins Company, 1932.

This is a book incorporating the results of ten years' research by a group of American investigators, carefully selected by the Committee on Research in Problems of Sex of the Division of Medical Sciences, National Research Council. Specialization in research has attained the point where any detailed authoritative survey requires a group effort. Consequently, the editor has gathered together a group of investigators whose work has established them in their respective fields. The body of the book is divided into nineteen chapters, and each contributor has developed his chapter in his own way, and assumes full responsibility for the content of his section, including his discussion of the work of other investigators.

At the onset it is admitted that a brief definition of the biologic conception of sex is impossible. Not "sex" but sexes are discussed, since there is no such biologic entity as sex. What exists in nature is a dimorphism within species into male and female individuals, which differ with respect to contrasting characteristics, for each of which in any given species is recognized a male and a female form, whether these characteristics are classed as of the biologic, psychologic or social order.

In the earlier chapters the genetics of sex is discussed. Riddle has an excellent contribution on metabolism and sex. Two chapters are then given over to the testis and its hormones. The editor's choice of subject is the "Ovarian Follicular Hormone, Theelin"; he discusses the results of its injection into lower animals, its substitutional value in ovariectomized animals, the vaginal reaction, its action on accessory genital organs, its function during pregnancy and its application to human welfare. Allen states that the principal function of theelin is to control the accessory genital organs, and that it apparently has little effect on the ovaries themselves. It is a temporary substitute rather than a cure for hypo-ovarian disorders. Doisy, who isolated and crystallized theelin, wrote the chapter on its biochemistry. Hisaw discusses the physiology of the corpus luteum as demonstrated by extracts. Inhibition of the estrous cycle and ovulation, mucification of the vaginal mucosa, relaxation of the pelvic ligaments of the guinea-pig and uterine effects in the nature of motility of the organ and progestational changes of the endometrium are dealt with in a routine manner. Turner devotes a chapter to the mammary glands, in which he deals with the effect of ovarian grafts, mammary growth during pregnancy and the physiology of lactation. The last half of his contribution is given over to experimental development of the mammary glands as influenced by the ovarian and anterior pituitary hormones, either singularly or in combination. The next chapter includes plumage tests on birds that have undergone gonadectomy or have received hormonal injections. Hartman deals with ovulation and the transport and viability of ova and sperm in the female genital tract. Smith discusses the effect of ablation and implantation of the anterior hypophysis on the reproductive system, and the influence of sex, the sex cycle and age on the pituitary content of the gonad-stimulating hormone. Engle's contribution presents the effects of extracts of the anterior pituitary and similar active principles of blood and urine during pregnancy on various animals of both the male and the female sex. In the latter part of the chapter he comments on the placenta as the probable source of the hormone, and the biologic implications favoring the concept of a single gonadokinetic substance in the anterior lobe. These last two authors discuss the effect of the thyroid and suprarenals on genital function. Stone has a chapter on sexual drive, while Pratt, the only contributor

who is a doctor of medicine, deals with the endocrine disorders in sexual function in man, and attempts to present a clinical application of the various hormones to sexual dysfunction.

This book deals predominately with a method of control of sex characteristics, which are especially related to vertebrates, mediated by hormones circulating in the blood. It is distinctly not a popular book on "sex," but should appeal to the scientifically minded student of problems of sex and of sexual functions in the lower animals. The internist and gynecologist will probably find many chapters too experimental for their interests, as all the contributors except one are essentially research workers. The bibliography at the end of each chapter offers an extensive field for reference and investigation in the study of the sex hormones.

The face print is monotype, number 31 E, Bruce oldstyle, and is appropriate because it is closely set and legible. The main text is 10 point. The illustrations are excellently displayed on a Cumberland English finish quality of paper, and the binding is in the T pattern of Interlaken extra colors.

The History of Dermatology. By William Allen Pusey, A.M., M.D., LL.D., Professor of Dermatology (Emeritus), University of Illinois; sometime President of the American Dermatological Association, and of the American Medical Association. Fabrikoid. Price, $3. Pp. 223, with 32 illustrations. Springfield, Ill.: Charles C. Thomas, 1933.

That Dr. Pusey would write an interesting book was a foregone conclusion, but that he could cover the field so well in such a short work and not have a mere recitation of names, figures and facts is remarkable. The book is divided into two parts.

The first part, of 175 pages, deals with the history of dermatology from the pre-Hellenic age to the present. Ancient, medieval, and early modern dermatology is treated adequately, but most of this part is concerned with the modern phase, after 1800. The early individualistic British are exemplified by Willan and Bateman; then followed the ascendency of the French school, which grew up about the St. Louis Hospital, which in 1801 became an exclusive dermatologic institution. Alibert, Biett Gibert, Devergie and Bazin are the outstanding figures delineated. The leadership soon passed to Germany, because there medicine became a part of university organization. While earlier Germans did much excellent work, the contributions of Hebra and Kaposi served to give preeminence to the Vienna school. Scandinavian, Italian, later French (Besnier, Vidal, Hallopeau and Brocq), later English (Wilson, T. Fox, Hutchinson and Crocker) and Continental (Neisser, Unna and Finsen) contributors receive adequate consideration.

American dermatology is not forgotten. Bulkley, Worchester, James C. White, Piffard, Duhring, Hyde, Hardaway and George Fox form part of the roll of distinguished American dermatologists whom the author mentions. Of more than special interest is the resurrection of an almost forgotten pioneer American dermatologist, Noah Worchester, who in 1845 published a 292 page text on "Diseases of the Skin," the first American book of its sort.

The history is developed mostly by individual biographical sketches. Each sketch, complete in itself, fits into the whole to form a finished picture. The relationship of dermatology to other fields of medicine, syphilology and the founding of societies and journals is also considered.

The second part, of 36 pages, is an alphabetical index of all, rare and common, conditions of the skin with the name and date of the first describer and an easily obtained reference where a bibliography and discussion of the subject may be found. This historical glossary represents an immense amount of bibliographical work condensed into a brief and easily available form. The work was chiefly done by the author's associate, Dr. Herbert Rattner.

The book is well bound, the paper is of good quality, the type is large and easily read, the illustrations are excellent, the proof-reading is good, and the general lay-out is a credit to the publisher.

No dermatologist should be without this book. Students of medical history will find it a short and complete exposition of the growth of dermatology, and general medical readers will enjoy Dr. Pusey's clear and readable style and obtain a background of dermatologic lore not previously obtainable in English. The author and the publishers are to be congratulated.

Diagnosis and Treatment of Diseases of the Thyroid Gland. By George Crile and Associates. Price, $6.50. Pp. 491. Philadelphia: W. B. Saunders Company, 1932.

Dr. Crile and twenty-three of his associates have contributed to this volume. It really amounts to a collection of papers on thyroid topics by members of a thyroid clinic. The chapters vary considerably in quality and cannot, when taken collectively, be said to cover in any comprehensive way the field implied by the title. The book as a whole lacks cohesiveness, and there are in it some rather striking lacunae. For example, one finds no adequate discussion of such an important subject as myxedema, either its diagnosis or its treatment. The arrangement of the work is rather trying for the reader who wishes to use it as a textbook. Topics are so scattered that it is hard to find anywhere in one place a full discussion of all the important aspects of either diagnosis or treatment of any of the important diseases of the thyroid.

The chapters on surgery by the elder Crile are the most important in the book. The wisdom acquired by this master surgeon in a colossal operative experience is here set forth with sufficient clarity. When he enters the field of biophysics, however, Dr. Crile becomes somewhat nebulous.

Of other chapters, those which impressed the reviewer most favorably were those of Dinsmore on "Hyperthyroidism in Children," Anderson on "Cardiac Disturbances Associated with Hyperthyroidism," Mullin on "Laryngeal Disturbances in Hyperthyroidism," John on "Carbohydrate Metabolism in Hyperthyroidism" and Nichols on "Roentgenological Observations in Thyroid Disease." It is a pity that this last mentioned excellent chapter does not cover all aspects of roentgenology of the thyroid.

Toward the end of the book is a chapter in which Dr. Crile gives his theories of the relation of the suprarenals to thyrotoxicosis. He claims to have obtained good results in a series of cases of hyperthyroidism by suprarenal denervation, but gives no detailed information by which the reader can evaluate the method for himself.

Lehrbuch der Histologie und Histogenese. By Dr. Univ. Med. Josef Schaffer, o. ö. Professor der Histologie an der Universität in Wien. Third edition. Price, 20 marks. Pp. 576, with 640 figures in the text (some in colors) and 14 additional full page colored plates (mostly lithographs). Leipzig: Wilhelm Engelmann, 1933.

This is a third and completely revised edition of a textbook that has been outstanding during the last twelve years. Several cuts have been replaced by better ones, and more than 70 new ones have been added. The 37 page section on microscopy of earlier editions has been eliminated to make room for new matter necessitated by advances in many lines, especially in the supporting tissues and endocrine organs. Histogenesis is carefully summarized after the adult structure of each tissue or organ has been described. The book is up to date and well illustrated. The type is clear and the paper good. Many composite diagrams, such as changes in the uterine mucosa during the menstrual cycle, are useful features. At the beginning of the book there is a selected list of 74 texts on microscopy, cytology, histology and histologic technic, and at the end is added a bibliography of original papers by about 650 authors.

The topics in the order of presentation in part I are: blood, cell division, epithelia (including glands in general), connective and supporting tissues (bone unusually complete) and muscular and nerve tissues (including general sensory and

motor endings). Part II discusses the special histology of the organs in the following order: vascular system and lymphoid organs, endocrine organs (thyroid, parathyroid, hypophysis, suprarenal, pineal, carotid and coccygeal bodies, islands of Langerhans, corpus luteum and interstitial cells of the testis), the skin and its appendages, digestive system, respiratory system, urinary system, male and female sex organs and special sense organs (visual, auditory and olfactory). It is a well balanced summary of microscopic anatomy and should continue to be widely used as a general text wherever the German language is spoken.

The Colon, Rectum and Anus. By Fred W. Rankin, M.D., J. Arnold Bargen, M.D., and Louis A. Buie. Price, $9.50. Pp. 846, with 435 illustrations. Philadelphia: W. B. Saunders Company, 1932.

This volume is concerned with the diagnosis and treatment of medical and surgical conditions of the large bowel and contains chapters on anatomy and physiology, and embryology of this region. As is to be expected, the greatest portion of the book is devoted to surgery, including operative procedure and choice of the anesthetic. The material presented is obtained from a study of the records of the Mayo Clinic plus a rather comprehensive review of the literature. At the end of each chapter is an excellent bibliography of the subject considered. Statistical data, obtained both from the authors' records and from the literature, are presented with considerable thoroughness.

Of especial interest to the reviewer are the sections on chronic ulcerative colitis and parasitic diseases of the large bowel. In the instance of the former, one is impressed with the idea that the writer feels he is presenting a subject that is going to be read with considerable skepticism, and an intense effort is made to be convincing. As in the past, his ideas as to etiology and treatment of this condition will be accepted with reservation. A great many excellent plates of the gross pathologic changes and a few of microscopic sections are to be found, though none are colored. There are numerous reproductions of x-ray plates of the colon in this chapter, as in practically all others. It seems strange that in considering the diagnosis of chronic ulcerative colitis not one plate of the proctoscopic picture is to be found. This applies to other conditions of the bowel as well, as only three sketchy proctoscopic pictures are found in the entire volume.

The authors are to be commended for the easy style and the well chosen English of the volume. Their ability to condense articles, while still retaining important facts, is amazing.

The Aetiology of Tuberculosis. Translated from the German of the original paper before the Physiological Society of Berlin, March 24, 1882, by Dr. and Mrs. Max Pinner. With an Introduction by Dr. Allen K. Krause. Cloth. Pp. 48. New York: National Tuberculosis Association.

This classic paper by Dr. Koch, announcing the discovery of the tubercle bacillus, presented before the Physiological Society of Berlin in 1882, is published by the National Tuberculosis Association marking the semicentenary of Koch's epoch-making achievement. The paper itself, recently translated from the German by Dr. and Mrs Max Pinner, is made far more interesting to the present-day reader by a sympathetic and illuminating introduction by Dr. Allen E. Krause. In the introduction, Krause outlines clearly the status of medical knowledge of half a century ago and reviews the scientific endeavors of Koch leading up to his final conclusions in such manner that the reader grasps the state of mind of the medical world when Koch announced his discovery.

The little volume includes a reproduction of the original article as it appeared in the *Berliner klinische Wochenschrift*, a portrait of Koch and other historic illustrations.